Journal of Biomedical Informatics 54 (2015) 167–173

Contents lists available at ScienceDirect

Journal of Biomedical Informatics

journal homepage: www.elsevier.com/locate/yjbin

Prediction of clinical risks by analysis of preclinical and clinical adverse events

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ARTICLE INFO

Article history:
Received 6 November 2014
Accepted 24 February 2015
Available online 5 March 2015

Keywords:
Bayesian
Translational medicine
Animal–human concordance
Adverse events
Drug risk
Likelihood ratio

ABSTRACT

This study examines the ability of nonclinical adverse event observations to predict human clinical adverse events observed in drug development programs. In addition it examines the relationship between nonclinical and clinical adverse event observations to drug withdrawal and proposes a model to predict drug withdrawal based on these observations. These analyses provide risk assessments useful for both planning patient safety programs, as well as a statistical framework for assessing the future success of drug programs based on nonclinical and clinical observations.

Bayesian analyses were undertaken to investigate the connection between nonclinical adverse event observations and observations of that same event in clinical trial for a large set of approved drugs. We employed the same statistical methods used to evaluate the efficacy of diagnostic tests to evaluate the ability of nonclinical studies to predict adverse events in clinical studies, and adverse events in both to predict drug withdrawal. We find that some nonclinical observations suggest higher risk for observing the same adverse event in clinical studies, particularly arrhythmias, QT prolongation, and abnormal hepatic function. However the lack of these events in nonclinical studies is found to not be a good predictor of safety in humans. Some nonclinical and clinical observations appear to be associated with high risk of drug withdrawal from market, especially arrhythmia and hepatic necrosis. We use the method to estimate the overall risk of drug withdrawal from market using the product of the risks from each nonclinical and clinical observation to create a risk profile.

1. Introduction

Nonclinical animal models have long been accepted as a means to examine both the efficacy and toxicity of drugs before administration to humans. The motivation has always been to reduce risk to humans by observing the outcomes in animals [1]. The desire for animal testing for toxicity was increased after public tragedies of the "Lash-Lure" case in which aniline eyelash dyes caused blindness, the toxicity associated with the formulation of sulfanilamide with ethylene glycol, and the teratogenic effects of thalidomide [2–4].

Animal models for toxicity have been shown to correctly represent human toxicities in many cases [5]. However there are relatively few statistical studies evaluating the concordance of nonclinical and clinical observations [6]. The study of 30 compounds in various species by Goldsmith et al found that animals well predicted the maximum tolerated dosages for clinical trials [7]. Fletcher examined 45 compounds and found a low concordance between animal and human adverse events [8]. The current canonical work in animal–human concordance for toxicity is the Olson study which examined animal and human toxicity of 150 compounds from a variety of therapeutic areas. In that work, the overall true positive animal–human concordance rate was 7% for rodent only, 36% for combination of rodent and non-rodent, 27% for single non-rodent species, and 70% for observation in any species [9]. Several other studies have been published since then with generally similar results [10–13]. However, the majority of the evidence for the efficacy of animal studies is based on true positives, with limited analysis of the false positives and false negatives [14,15].

Evaluation of the ability of animal models to predict human responses and toxicities is critical now that there are increasing pressures to reduce animal testing in favor of in-vitro and computational predictive methods [16]. In this work we compared data for drugs that have matched nonclinical and clinical data presented in FDA and EMEA submissions and analyze the results to measure the concordance between nonclinical and clinical adverse event observations. The human–animal concordance is measured using

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http://dx.doi.org/10.1016/j.jbi.2015.02.008
1532-0464/

Bayesian statistical methods similar to those used to evaluate the efficacy of diagnostic tests. In addition, we study the relationship between the events and eventual drug withdrawal to look for observations that are statistically correlated to drug failure.

2. Methods

2.1. Data sources

The PharmaPendium database from Elsevier was used to summarize the adverse events each selected MedDRA adverse classes reported for each drug, as shown in Fig. 1 [17,18]. PharmaPendium contains data for 3815 drugs or drug formulations. The data is mined from FDA and EMEA documents released in connection with drug approval, and is supplemented by data from Mosby's Drug Consult and Meyler's Side Effects of Drugs [19,20]. Of the drugs that appear in the database, 102 have been withdrawn from the market or relabeled, providing a limited set of failure results for statistical analysis. In this case each approved formulation was considered separately since it is possible for drug combinations to have different adverse events than the drugs alone. Fig. 1 shows an example of the raw data from PharmaPendium that summarizes the number of times arrhythmias were reported for each drug. Each value is linked to full reports of each observation, linked to the original submission documents. Post-marketing adverse event reports were not used in this study; only those reported in controlled clinical studies were used.

In order to eliminate dependence on the number of submissions and clinical studies of each drug for various indications, each value in the table was translated to an indicator variable of 1, if there was an observation of an event in the category, and 0 if there were none. This was done to avoid using the raw counts which may be dependent on the number of studies performed for a particular drug. The indicator denotes that the drug is reported at least once to cause the effect. These indicator values were then used for the analyses.

	clinical observation	no clinical observation
nonclinical observation	a	c
no nonclinical observation	b	d

cells contain count of drugs in each category for the given class of adverse events

Fig. 2. 2 × 2 Contingency table used for statistical analysis.

2.2. Bayesian statistics

Bayesian statistics were used with a 2 by 2 contingency table to measure the relationship between two sets of observations – the relationships between nonclinical and clinical observations for adverse events or adverse event categories, and separately, combined nonclinical/clinical observations with drug withdrawal (see Fig. 2). We treat the nonclinical observation as a diagnostic test for the clinical observation and use the statistical methods developed for evaluation of the efficacy of diagnostic tests. The same analysis is applied to measure the relationship between adverse event observation and drug withdrawal.

The values in the 2 by 2 contingency table, which are counts of number of compounds in each of the four categories for a given biomedical observation or MedDRA class of observations, were generated as follows:

(a) Count of drugs for which the event was observed in both nonclinical and clinical studies – true positives.

Cardiac arrhythmias

Drugs *:

- View by drug class
- **Viewing by name**

	Preclinical Data view all 881	Clinical Data view all 26073	Post-Marketing Reports (AERS) view all 284208
1-13C-Caprylic Acid	2	no data	no data
Abacavir Sulfate	no data	3	244
Abacavir Sulfate; Lamivudine	no data	1	58
Abacavir Sulfate; Lamivudine; Zidovudine	no data	no data	71
Abarelix	2	no data	13
Abatacept	no data	11	129
Abciximab	no data	5	458
Abetimus Sodium	no data	1	no data
Abiraterone Acetate	2	70	76
Acamprosate Calcium	11	1	20
Acarbose	no data	1	43
Acebutolol Hydrochloride	1	41	60
Acecainide	1	1	no data

Fig. 1. PharmaPendium summary of adverse events.