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Improving drug safety with a systems pharmacology approach

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ABSTRACT

Systems pharmacology is used to mechanistically analyze drug-adverse drug reaction (ADRs) pairs and is a promising solution to the complex problem of understanding mechanisms of toxicity. In this research, we have explored the feasibility of retrospectively mapping population-level adverse events from the FDA Adverse Event Reporting System (FAERS) to chemical and biological databases to identify drug safety signals and the underlying molecular mechanisms. We used an analytic platform – Molecular Analysis of Side Effects (MASE™). For this purpose, we selected the adverse event of severe and potentially fatal cutaneous reactions (SCARs) that are associated with acetaminophen (APAP). SCARs encompass the continuum between Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). We found a statistically significant association between APAP and TEN, the most severe form of SCARs. We also explored the influence of APAP on other classes of drugs commonly associated with SCARs. We found that APAP significantly reduced the risk of SCARs commonly associated with carbamazepine (CBZ). We used molecular docking simulations to propose a mechanism for APAP's reduction in CBZ-induced SCARs which is competitive inhibition of the binding of CBZ to HLA-B*15:02. We conclude that systems pharmacology can complement established surveillance methodologies by providing a means to undertake an independent investigation and review of the mechanisms by which drugs cause adverse events.

1. Introduction

Adverse drug reactions (ADRs) cause substantial morbidity and mortality resulting in treatment costs in the billions of dollars (Ernst and Grizzle, 2001; Bates et al., 1997). Serious ADRs at therapeutic drug doses are rare (1:1000 to 1:10,000) and are often discovered after regulatory approval because of the small pre-approval safety databases and the broader population for which a drug is used or prescribed. It is estimated that there are up to 4.5 million drug-induced serious ADRs annually resulting in 1.9 hospitalizations (Sarkar et al., 2011; Lucado et al., 2011). It is clear that additional steps need to be taken to achieve incremental improvements in drug safety. We believe that new approaches are needed to better understand the molecular mechanisms of adverse events and to potentially apply this knowledge to predict ADRs before they occur based on targets and pathways.

In the United States, post-market surveillance is primarily performed by the Food and Drug Administration (FDA) using drug-centric data from its Adverse Event Reporting System (FAERS). FAERS is a rich source of ADR information submitted voluntarily by drug manufacturers, healthcare professionals and consumers. Each ADR report is evaluated by clinical reviewers in either the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) (Center for Drug Evaluation and Research, 2016). FAERS data are used for statistical data mining with such goals as: (Ernst and Grizzle, 2001) to enable investigations of newly reported drug safety issues, (Bates et al., 1997) to inform hypotheses about plausible causes of ADRs, and (Sarkar et al., 2011) to support regulatory actions such as label updates or market withdrawals (Tatonetti et al., 2012; Szarfman et al., 2002; Hauben et al., 2007). However, despite its well-documented usefulness, data mining of FAERS has widely recognized limitations such as under-reporting of ADRs, difficulties in estimating the prevalence of drug-ADR associations, and uncertainty that a given ADR is causally related to the perpetrator drug.

In this research, we devised a systems pharmacology approach by combining FAERS data-mining with highly curated knowledge about a perpetrator drug's on- and off-target pharmacology and its target and pathway interactions, where the on-target pharmacology is defined as an extension of an on-target desirable effect and the off-target pharmacology is the toxicity event induced form a downstream function of the target and is an unexpected spontaneous event. Systems pharmacology allows molecular transformation of clinical safety information to investigate ADRs mechanistically via the underlying drug-induced molecular

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perturbations in pharmacological targets and pathways (Cheng and Zhao, 2014; Kuhn et al., 2013). We believe that systems pharmacology can markedly improve drug safety in four ways: (Ernst and Grizzle, 2001) by enabling a more detailed and mechanistic understanding of ADRs that can provide feedback on how to mitigate future risks with the perpetrator drug or related molecules, (Bates et al., 1997) by rendering causal hypotheses and identifying biomarkers that can be used to predict ADRs before they occur, (Sarkar et al., 2011) by delineating a strategy for targeting high risk adverse events in clinical or post-marketing surveillance analysis, and (Lucado et al., 2011) by stratifying a population at the molecular level to identify risks for a particular ADR(Zhang et al., 2015; Ganter et al., 2008; Cheng et al., 2013a; Cheng et al., 2013b).

Severe cutaneous adverse reactions (SCARs) are serious and potentially fatal events occurring shortly after commencing therapy with a wide number of drug classes including anticonvulsants, antibiotics and nonsteroidal anti-inflammatories. SCARs is a term used to describe the continuum between relatively mild erythema multiforme (EM), Stevens-Johnson Syndrome (SJS) and the most severe reaction of Toxic Epidermal Necrolysis (TEN). It is difficult to differentiate SJS from TEN and therefore SCARs is often referred to as SJS/TEN (Becker, 1998; Mockenhaupt, 2009) SJS/TEN is most commonly thought to be a T-cell, immune-complex mediated hypersensitivity reaction(Hauben et al., 2007) although other pharmacological mechanisms, such as inhibition of COX isoenzymes, cannot be ruled out. With SJS/TEN, a patient's skin and mucous membranes react severely, and patients get flu-like symptoms which are followed by a painful rash that spreads and blisters, eventually causing the top layer of the skin to die off and shed. Drugs most commonly associated with SJS/TEN include allopurinol, nonsteroidal anti-inflammatory drugs (i.e., COX-2 inhibitors), anticonvulsants (e.g., carbamazepine), varenicline, sulfonamides and penicillins (Mockenhaupt, 2009; Levi et al., 2009; Mockenhaupt et al., 2008). In addition, recent warnings about drug-induced SJS/TEN from the FDA and the Canadian Health Protection Agency included clobazam and capecitabine.

In August 2013, the FDA released a safety communication regarding reports of rare but serious cutaneous reactions associated with acetaminophen (APAP), a common ingredient of widely used prescription and non-prescription products (http://www.fda.gov/drugs/drugsafety/ucm363041.htm). The FDA found 107 cases of SJS/TEN from 1969 to 2012 after a search of FAERS. Most cases involved single-ingredient APAP products. Manufacturers were subsequently required to add warning statements regarding severe skin reactions to their labels. We therefore selected APAP-SJS/TEN as a prototype drug:ADR pair to evaluate a systems pharmacology approach to drug safety. SJS/TEN will be used throughout this paper to describe the spectrum of SCARs to APAP because differentiation between SJS and TEN is not always possible within FAERS.

2. Materials and methods

2.1. Molecular Analysis of Side Effects (MASE™)

Systems pharmacology approaches to date have relied upon a variety of different software and data resources for hypothesis development and exploring the possible interactions between drugs, targets and pathways. We used a commercially available data warehouse platform (Molecular Analysis of Side Effects, MASE™, Molecular Health, Heidelberg, Germany). The MASE data warehouse has drug-centric content and an analytics platform that integrates drug:ADR reports from the publically available FAERS database (e.g., containing medications, therapy, dates, and patient characteristics), with drug-specific information (e.g., structures, synonyms, targets, and interactions) and other molecular level information (e.g., protein domains, pathways) in order to define molecular mechanisms and explanations for a given ADR. MASE™ can be queried to analyze ADRs and clinical outcomes associated with specific combinations of drugs, targets, metabolizing enzymes, pathways and disease indications. MASE™ can also be used to build and compare patient cohorts with respect to comparative drug safety. Beyond MASE™, we used additional software (e.g. SAS) that was uniquely selected based on the research questions at the different stages of our investigation. This software is described below. The following analysis was performed using MASE™ and an overview of the workflow for the evaluation of

APAP-SJS/TEN is shown in Fig. 1.

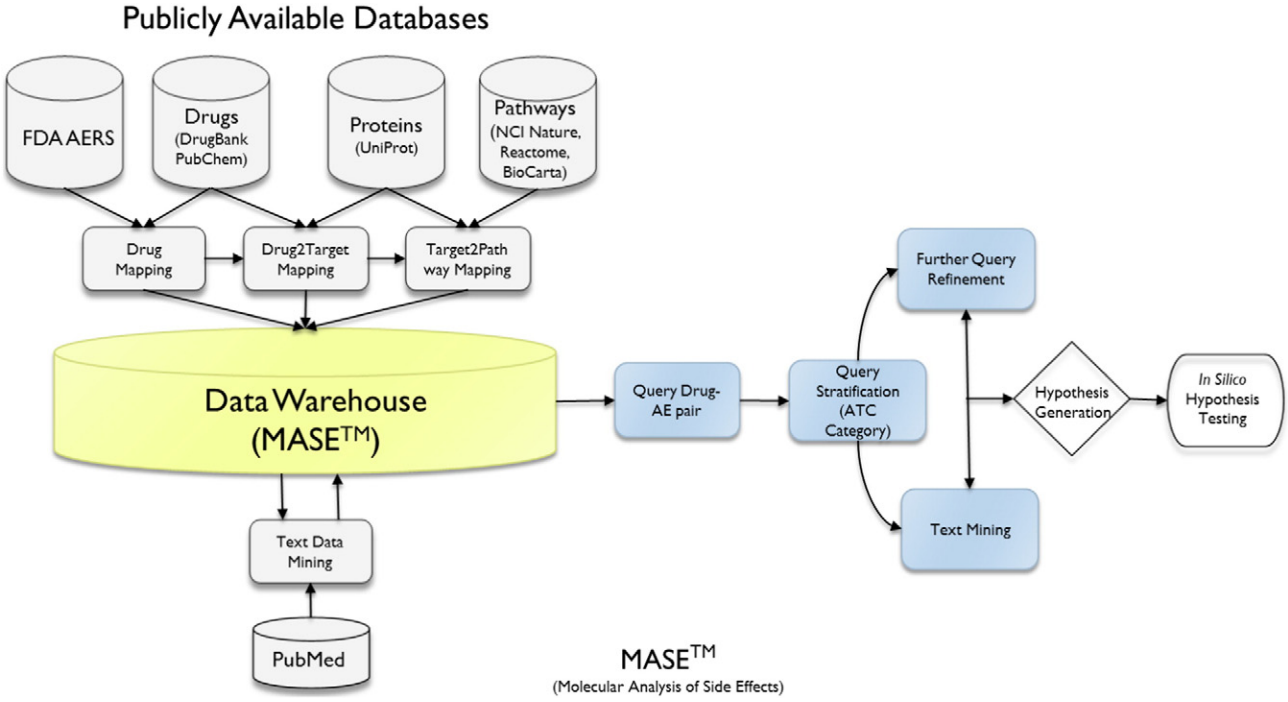

Fig. 1. Overview of analysis workflow for the evaluation of a drug: adverse event pairs. MASE™ (Molecular Analysis of Side Effects) is a clinically focused data warehouse integrating diverse data sources relevant to the investigation of the molecular mechanisms underlying adverse drug reactions. After identification of a drug-AE pair of interest, an iterated series of query and hypothesis refinements is followed by hypothesis testing in silico.