参考資料1

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ORIGINAL REPORT

Early detection of adverse drug events within population-based health networks: application of sequential testing methods[†,‡]

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SUMMARY

Purpose Active surveillance of population-based health networks may improve the timeliness of detection of adverse drug events (ADEs). Active monitoring requires sequential analysis methods. Our objectives were to (1) evaluate the utility of automated healthcare claims data for near real-time drug adverse event surveillance and (2) identify key methodological issues related to the use of healthcare claims data for real-time drug safety surveillance.

Methods We assessed the ability to detect ADEs using historical data from nine health plans involved in the HMO Research Network's Center for Education and Research on Therapeutics (CERT). Analyses were performed using a maximized sequential probability ratio test (maxSPRT). Five drug-event pairs representing known associations with an ADE and two pairs representing 'negative controls' were analyzed.

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[†]Dr Brown, Dr Kulldorff, Dr Davis, Dr Graham, Dr Raebel, Dr Boudreau, Dr Roblin, Dr Gurwitz, Dr Platt and Dr Gunter and Mr Pettus report no conflict of interest. Dr Chan, Dr Andrade, Dr Herrinton and Dr Smith report receiving industry research funding on issues unrelated to the study.

[‡]Dr Platt has included Figure 3 from this manuscript as an example of active surveillance in the following recent presentations: (1) IOM Forum on Drug Safety (12 March 2007), The Future of Drug Safety—Challenges for the FDA (Drug Safety Symposium, The National Academies, IOM), (2) IOM-FDA meeting (24 April, 2007), Emerging Safety Science: A Forum on Drug Discovery, Development and Translation and (3) Keynote address at AMIA workshop on drug safety (13 June 2007), American Medical Informatics Association, Invitational Conference on Drug Safety and Pharmacovigilance.

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Results Statistically significant ($p < 0.05$) signals of excess risk were found in four of the five drug-event pairs representing known associations; no signals were found for the negative controls. Signals were detected between 13 and 39 months after the start of surveillance. There was substantial variation in the number of exposed and expected events at signal detection.
Conclusions Prospective, periodic evaluation of routinely collected data can provide population-based estimates of medication-related adverse event rates to support routine, timely post-marketing surveillance for selected ADEs. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — adverse drug event; methodology; sequential analysis; drug safety surveillance; SPRT

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INTRODUCTION

Current prospective post-marketing drug monitoring in the U.S. relies principally on passive surveillance via MedWatch reports to the Adverse Event Report System (AERS).[1–3] Passive monitoring systems have well-recognized drawbacks, including underreporting, reporting bias, incomplete data and limited information on the exposed population and a lack of denominators, thereby making it difficult to know if the spontaneous reports represent an increase in incidence over baseline.[1,4] Additionally, passive surveillance systems cannot provide quantitative information about the frequency or relative risk of reported reactions. These problems are particularly troubling for reported adverse reactions that are also common occurrences in the absence of the drug exposure.

Active surveillance of health plans' populations may improve the timeliness of detection of adverse drug events (ADEs). To realize the full potential of prospective surveillance, the accumulated drug exposure and event experience should be evaluated as it accumulates. Frequent prospective monitoring requires new capacity for extracting information from healthcare data systems, for aggregating information from multiple sources and for analyzing this information in a manner that avoids problems associated with repeated statistical tests on the same data. The CDC sponsored Vaccine Safety Datalink (VSD) has described such a prospective monitoring system for adverse vaccine reactions, using data from eight health plans.[5,6] Applying this methodology to surveillance for ADEs is considerably more complicated than it is for vaccines, in part because many drug exposures are chronic or intermittent, in contrast to vaccines which are usually administered only once or twice. In addition, risk windows for drug exposure may vary considerably by drug type and length of exposure.

This report describes our application of sequential analysis within a well-defined population to detect ADE signals. The goals were to use historical data to (1) evaluate the utility of automated healthcare claims data for near real-time drug adverse event surveillance and (2) identify key methodological issues related to the use of healthcare claims data for real-time drug safety surveillance.

METHODS

Overview

We assessed the ability of sequential analysis to detect ADEs using historical data from nine health plans involved in the HMO Research Network's Center for Education and Research on Therapeutics (CERT).[7] Multiple drug-event pairs were selected for analysis. We define a 'signal' as a statistically significant association between a drug and selected diagnosis codes that requires further attention to determine causality.[8] Key findings regarding the performance of the methodology are reported and key methodological issues are discussed.

Study population and data source

The study cohort was drawn from health plan members who were enrolled at any time from 1 January 2000 to 31 December 2005 in one of the nine health plans involved in the HMO Research Network CERT. The nine health plans are located in different geographic regions across the U.S.

Each of the nine participating health plans created four datasets corresponding to demographic, health plan enrollment, dispensing and diagnosis information based on specifications provided by the study coordinating center for the period 1 January 2000 through 31 December 2005. The demographic file contained date of birth and sex and the enrollment file contained start and stop dates for health plan enrollment and an indicator for whether or not the

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member had drug coverage during the enrollment period. The dispensing file contained all dispensing records for the cohorts of interest and included dispense date, national drug code for the dispensing, units dispensed, days supplied and generic name. The diagnosis file contained records for all ambulatory and inpatient diagnoses recorded on health plan automated claims, including each ICD-9-CM code recorded, date of diagnosis and an indicator for whether the care was provided in an inpatient or outpatient setting.

All health plan members who had at least one membership period with drug coverage of greater than 270 days were included in the analyses. Membership gaps of 60 days or less were bridged to create continuous membership periods. For analytic simplicity, only the first valid membership period was used. The study was approved by the human subjects committees at each health plan.

Drug-event pairs and comparisons

We constructed seven drug-event pairs to assess the stability and performance characteristics of the methodology (Table 1). The drug-event pairs were selected by the authors in 2003 and 2004. Five of the drug-event pairs were selected as known associations between a drug and a serious ADE and two were selected as negative controls for which no association was expected. There were at least two comparison cohorts for each drug-event pair: (a) all health plan members who did not use the drug of interest (non-users) and (b) all health plan members who were incident users (defined below) of a pre-selected comparison drug or drug class. The comparison to non-users was included because active comparators are not commonly available in other safety surveillance and data mining activities (e.g., AERS analyses) and it is expected that future active surveillance studies might involve drugs with no relevant comparator.

Calculating observed and expected counts

We performed analyses that simulated monthly prospective surveillance. For each month the maximized sequential probability ratio test (maxSPRT) requires information about the number of observed adverse events during the month and the expected number under the assumption that the null hypothesis of no excess risk is correct.

Definition of incident exposure. This study focused on incident users of the drug of interest or the comparator agent.[9] Incident use was defined as a dispensing for which there was no other dispensing of the drug of interest or a comparator drug during the prior 181 days (i.e., 181-day exposure-free period). Members who failed to meet the incident dispensing criteria, either due to continuous drug exposure or insufficient membership time, were excluded from the relevant comparison drug analyses. Multiple incident dispensings during the membership period were allowed as long as the requirement of a 181-day exposure-free period was satisfied.

Definition of incident outcome. To be considered an ADE, the diagnosis code of interest was required to be assigned in an inpatient setting; this need not be a criterion for use of this technique, but was adopted for this demonstration to improve the likelihood of detection of serious occurrences. Additionally, these events had to meet our incident ADE criteria that we defined as having no observed inpatient or outpatient

Table 1. Listing of all comparisons included in the evaluation

Drug of interest	Drug comparators	Outcome	Definition of outcome*
Celecoxib	Diclofenac, naproxen	Acute myocardial infarction	Acute myocardial infarction: 410.xx
Rofecoxib	Diclofenac, naproxen	Acute myocardial infarction	Acute myocardial infarction: 410.xx
Valdecoxib	Diclofenac, naproxen	Acute myocardial infarction	Acute myocardial infarction: 410.xx
Lisinopril	ARBs	Angioedema	Angioedema: allergic, any site, with uticaria: 995.1
Cerivastatin	Other statins	Rhabdomyolysis	Rhabdomyolysis: 728.89
Cetirizine**	Fexofenadine and loratadine	Thrombocytopenia	Thrombocytopenia: 287.4 and 287.5
Clemastine**	Loratadine	Stevens–Johnson syndrome, toxic epidermal necrolysis	Erythematous conditions: 695.0 toxic erythema; 695.1 erythema multiforme

*Diagnosis codes based on ICD-9-CM classifications. Based on the study criteria, only inpatient diagnoses were included as adverse events.
**These represent negative controls; no association between the drug and event was expected.
ARBs, angiotensin II antagonists.

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