SHORT COMMUNICATION

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Prospective Drug Safety Monitoring Using the UK Primary-Care General Practice Research Database

Theoretical Framework, Feasibility Analysis and Extrapolation to Future Scenarios

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Abstract

Background: Post-launch drug safety monitoring is essential for the detection of adverse drug signals that may be missed during preclinical trials. Traditional methods of postmarketing surveillance such as spontaneous reporting have intrinsic limitations, many of which can be overcome by the additional application of structured pharmacoepidemiological approaches. However, further improvement in drug safety monitoring requires a shift towards more proactive pharmacoepidemiological methods that can detect adverse drug signals as they occur in the population.

Objective: To assess the feasibility of using proactive monitoring of an electronic medical record system, in combination with an independent endpoint adjudication committee, to detect adverse events among users of selected drugs.

Methods: UK General Practice Research Database (GPRD) information was used to detect acute liver disorder associated with the use of amoxicillin/clavulanic acid (hepatotoxic) or low-dose aspirin (acetylsalicylic acid [non-hepatotoxic]). Individuals newly prescribed these drugs between 1 October 2005 and 31 March 2006 were identified. Acute liver disorder cases were assessed using GPRD computer records in combination with case validation by an independent endpoint adjudication committee. Signal generation thresholds were based on the background rate of acute liver disorder in the general population.

Results: Over a 6-month period, 8148 patients newly prescribed amoxicillin/clavulanic acid and 5577 patients newly prescribed low-dose aspirin were identified. Within this cohort, searches identified 11 potential liver disorder

cases from computerized records: six for amoxicillin/clavulanic acid and five for low-dose aspirin. The independent endpoint adjudication committee refined this to four potential acute liver disorder cases for whom paper-based information was requested for final case assessment. Final case assessments confirmed no cases of acute liver disorder. The time taken for this study was 18 months (6 months for recruitment and 12 months for data management and case validation). To reach the estimated target exposure necessary to raise or rule out a signal of concern to public health, we determined that a recruitment period 2–3 times longer than that used in this study would be required. Based on the real market uptake of six commonly used medicinal products launched between 2001 and 2006 in the UK (budesonide/eformoterol [fixed-dose combination], duloxetine, ezetimibe, metformin/rosiglitazone [fixed-dose combination], tiotropium bromide and tadalafil) the target exposure would not have been reached until the fifth year of marketing using a single database.

Conclusions: It is feasible to set up a system that actively monitors drug safety using a healthcare database and an independent endpoint adjudication committee. However, future successful implementation will require multiple databases to be queried so that larger study populations are included. This requires further development and harmonization of international healthcare databases.

Background

Post-launch drug safety monitoring has traditionally been based upon the collection and analysis of reports submitted spontaneously by health professionals (and, in some countries, also consumers).[1] The use of spontaneous reporting data to generate hypotheses regarding potentially rare and serious adverse drug reactions remains an essential component of drug surveillance strategies; however, spontaneous reporting is limited in its ability to accurately quantify drug safety signals.[2] This limitation can be complemented by the additional application of more structured pharmacoepidemiological methods (e.g. cohort studies and case-control studies), which allow incidence estimates of adverse outcomes in people taking a drug to be compared with the general population.[3] Further improvement in drug safety monitoring requires a switch towards pharmacovigilance planning that involves more proactive use of pharmacoepidemiological methods to detect adverse drug signals.[4] Such approaches have recently been recommended by both US and European guidelines on risk management.[5-7]

Proactive drug safety monitoring relies on having complete data, from sufficient patient numbers, in as timely and accurate a manner as possible. Automated healthcare databases may be ideally suited to this task and have already been widely used as an efficient data source for conducting pharmacoepidemiological studies.[2] If these databases were accessed regularly, they could also be used to carry out prospective active surveillance for the early detection of risks associated with new drugs.

Here, we describe the theoretical framework and test the feasibility of a system designed to proactively detect and quantify the presence of drug-associated acute liver disorder. The feasibility of this framework was tested by actively monitoring patient data from the UK General Practice Research Database (GPRD) in combination with case validation by an independent endpoint adjudication committee based on the review of patients' medical charts. We chose to use acute liver

disorder as our outcome measure because it is frequently associated with pharmacovigilance signals involving new drugs. We aimed to measure this outcome relative to exposure to a drug known to be hepatotoxic (amoxicillin/clavulanic acid) and to a non-hepatotoxic drug (low-dose aspirin [acetylsalicylic acid]). In performing this study, we hoped to estimate the time required to achieve such proactive surveillance, particularly with regard to practicalities such as logistics, data collection and case evaluation. Importantly, this study would also provide information on the minimum follow-up period required to detect or rule out a signal concerning serious liver disorders when using a primary-care database.

Methods

The present study was divided into two phases: first, we tested the logistics of working proactively using an automated database; and second, we estimated the resources necessary for such a signal generation system to be applied in the future.

Logistics Testing

Data Source

We used the GPRD as our source of patient information. This database contains medical information on nearly 3 million patients and is regularly updated by primary-care practitioners (PCPs) in a standardized fashion. The data cover patient demographics, all medical diagnoses and prescriptions, and consultant and hospital referrals. Diagnoses are coded using the Oxford Medical Information System (OXMIS) and Read dictionaries, which can be partially mapped to codes from the International Statistical Classification of Diseases and Related Health Problems, 8th revision (ICD-8). In addition, all prescriptions are generated by computer and automatically recorded using a code based on the Prescription Pricing Authority (now known as NHS Prescription Services) dictionary. A previous study using the GPRD documented that 90% of the referral codes entered by PCPs into their computers reflect the consultant diagnosis.[8] Primary healthcare practices contributing to the GPRD are widely distributed across the UK and include all segments of the population, as is evidenced by similar age and sex distributions in the GPRD compared to UK census data. The accuracy and completeness of the GPRD have been validated in previous studies.[9-11] Information from the GPRD is de-identified, organized and managed by the Medicines and Healthcare Products Regulatory Agency (MHRA) for use in research projects.

Study Population Inclusion and Exclusion Criteria

Most drug-related acute liver disorders tend to occur within the first 3 months of exposure.[12] Therefore, we decided to select only new users of selected drugs for this study. The study population consisted of patients aged 20–79 years who had been newly prescribed (i.e. no recorded use during 1 year before) amoxicillin/clavulanic acid or low-dose aspirin between the target period of 1 October 2005 and 31 March 2006. All of these individuals had been enrolled with a PCP for at least 2 years and had a computerized prescription history covering at least 1 year.

Subjects with an outcome code consistent with acute liver disorders (see Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A23) before the target period were excluded from the study. Subjects with cancer, acquired immune deficiency syndrome, infectious hepatitis, chronic liver disorders, gallbladder disease, pancreatitis, or alcoholism at any time before their first prescription were also excluded.

Procedures and Outcomes

During the target period, a standing query was set up with the GPRD in which data files from individuals newly prescribed amoxicillin/clavulanic acid or low-dose aspirin were identified every 3 months and sent to the principal investigator (i.e. two sets of profiles were sent between 1 October 2005 and 31 March 2006). A computerized search was performed within this cohort by the Spanish Centre for Pharmacoepidemiological Research (CEIFE) to identify data files for individuals aged 20–79 years with one of the codes suggesting liver disorders but without any of the exclusion criteria ('computer cases').

Non-case:
- the outcome was clearly not idiopathic liver disorder or the patient was not referred to a consultant or a hospital
  or
- one of the following was present: normal liver function tests or minor elevations in liver function tests (<2 × ULN), viral infection (confirmed with serological tests), cholelithiasis or the presence of any other well defined pathology known to cause acute liver disorder

Potential case based on computer code:
- the information recorded on the computer was compatible with acute liver disorder

Fig. 1. Criteria for defining patients as either non-cases or potential cases of acute liver disorder. **ULN** = upper limit of the normal range.

Computerized patient profiles (without related free-text comments) from these computer cases were subsequently sent for review by an external board of experts comprising three members: Dr Francisco de Abajo, Professor Roger Jones and Professor Rolf Olsson. Based on this review, patients were defined as either non-cases or potential cases of acute liver disorder, according to the criteria described in figure 1. After a review of the computerized patient profiles, de-identified medical records were requested by the board of experts (via the GPRD) for all individuals still considered by at least two board members potentially to have acute liver disorder. Similarly, if at least two members of the board required additional information to make a final case assessment, then a questionnaire was sent (via the GPRD) to the patient's PCP. Once all paper-based information was received and reviewed by the external board, a final agreement was reached regarding whether any of the patients had acute liver disorders. General criteria for determining whether there were acute liver disorders were provided to the external board[13] (figure 2) and were used in combination with their expert opinion.

Estimation of Resources Required

We estimated the number of new patients needed in order to detect acute liver disorder as a signal of public health importance. This would allow us to determine the follow-up time required in a single database depending on the market uptake of a given medicinal product.

Based on previous studies which used the same case selection criteria,[14-16] we estimated a background incidence of one case of liver disorder requiring referral or hospitalization per 50 000 new users of a medicinal product. In the current analysis, a signal was considered of public health importance if the incidence of acute liver disorder was at least 10-fold higher than the background rate (i.e. ≥1 per 5000 new users). The threshold for generating a signal of clinically relevant acute liver disorder was set at three confirmed cases in a target cumulative exposure of 15 000 new users (or lower if the three cases were detected earlier). If one or two confirmed cases of acute liver disorder were detected, the need for extending the recruitment period would be considered. Conversely, according to the 'rule of three',[17] if no confirmed cases were detected, this would indicate with 95% confidence that the acute liver disorder incidence was not greater than 1 in 5000 new users of the drug.

The potential of a primary-care database to detect a signal associated with a new drug would depend on two factors: (i) the target incidence of the specific adverse event (which is a result of the predefined estimate of relative risk and the background incidence of this event); and (ii) the uptake of the study product within the database. To have an idea of the real uptake of new drugs in a primary-care database we obtained data from The Health Improvement Network (THIN) on the cumulative number of new users for six commonly used medicinal products launched between 2001

Patients were defined as having liver disorder if they presented with:
- an increase in ALT of >2 × ULN
  or
- a combined increase in AST, AP and total bilirubin, provided one of them was ≥2 × ULN

Liver disorder was designated as:
- hepatocellular, when there was an increase in ALT alone of >2 × ULN or when R ≥ 5, where R is the ratio of serum activity of ALT over serum activity of AP
- cholestatic, when there was an increase in AP alone of >2 × ULN or when R ≤ 2
- mixed, when 2 < R < 5

Liver disorder was considered acute if:
- symptoms completely disappeared after 6 months

Fig. 2. General criteria for determining whether there was acute liver disorder that were provided to the external board and used in combination with their expert opinion[13] **AP** = alkaline phosphatase; **ULN** = upper limit of the normal range.

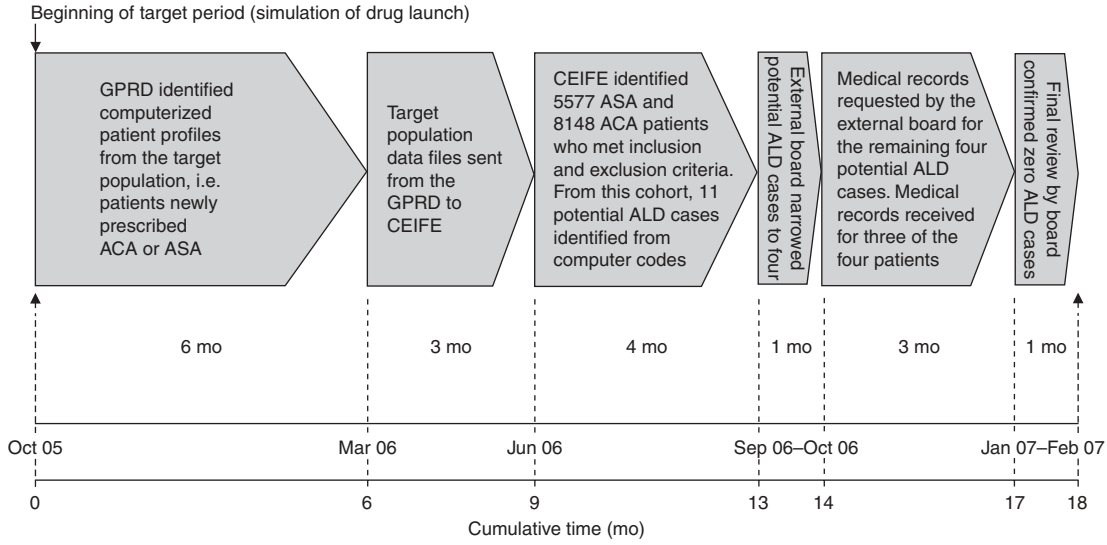

Fig. 3. Timeline of the feasibility study. **ACA** = amoxicillin/clavulanic acid; **ALD** = acute liver disorder; **ASA** = low-dose aspirin (acetylsalicylic acid); **CEIFE** = Spanish Centre for Pharmacoepidemiological Research; **GPRD** = General Practice Research Database.

and 2006 in the UK: budesonide/eformoterol (fixed-dose combination), duloxetine, ezetimibe, metformin/rosiglitazone (fixed-dose combination), tiotropium bromide and tadalafil. THIN is a UK-based primary-care database containing medical information for over 3 million people, essentially similar to the GPRD.

Results

The steps implemented throughout this study are shown in figure 3. All data files from patients newly prescribed amoxicillin/clavulanic acid or low-dose aspirin between 1 October 2005 and 31 March 2006 were received at CEIFE by the end of June 2006. By the end of July 2006 searches had been performed at CEIFE to narrow this group down to individuals aged 20–79 years who did not meet any of the exclusion criteria.

The searches performed by the GPRD and CEIFE over a 6-month period identified 5577 patients who had been newly prescribed low-dose aspirin and had received a total of 15 171 prescriptions, and 8148 patients who had been newly prescribed amoxicillin/clavulanic acid and had received a total of 9254 prescriptions. The principal investigator identified six potential cases of acute liver disorder in the amoxicillin/clavulanic acid cohort and five potential cases in the aspirin cohort. All eleven computerized patient profiles (without free-text comments) were sent to the external board of experts for review by early September 2006.

Provisional case status assignments, based on a review of the computerized information by the board of experts, were finalized by mid October. Further paper-based information was requested from PCPs if a patient was still considered by at least two of the three experts to be a potential case of acute liver disorder. This process resulted in four cases being forwarded to the GPRD with a request for the associated medical records. By early January 2007 three of the four medical records requested had been received by the principal investigator and sent to the board of experts. In early February, finalized case status assignments were received from all three experts. None of the three individuals for whom paper-based information was available met the case definition criteria (by unanimous decision). The remaining individual, for whom additional information had not been received, was not given a final case assessment by two of the experts. The third expert did not request medical records for this patient because he did not consider them to be a potential

Table I. Review process undertaken by the board of experts to identify cases of drug-associated acute liver disorder

Case no.	Expert 1 case status notes	Expert 1 further information	Expert 2 further information	Expert 3 further information	Information from PCP	Expert 1 final review	Expert 2 final review	Expert 3 final review
1	No case (slightly high γ GT, one isolated result of 2 × ULN ALT, reversible)	No	No	No	Not requested	NA	NA	NA
2	No case (high γ GT, ALT <2 × ULN)	No	No	Yes	Not requested	NA	NA	NA
3	No case (slightly high γ GT)	No	No	No	Not requested	NA	NA	NA
4	No case (high γ GT, ALT 2 × ULN, alcohol-related)	No	Yes	Yes	Requested but not received	No case – minor elevations, no referral	NA	NA
5	No case (high γ GT, ALT <2 × ULN, alcohol-related)	No	No	Yes	Not requested	NA	NA	NA
6	Potential case (jaundice – bile stones to be ruled out)	Yes	Yes	Yes	Requested and received	No case – cholangiocarcinoma	No case – cholangiocarcinoma	No case
7	No case (γ GT high, ALT <2 × ULN, alcohol-related)	No	Yes	No	Not requested	NA	NA	NA
8	Doubtful (liver function abnormal, no data; acute delirium organic, alcohol-related?)	Yes	Yes	No	Requested and received	No case – minor elevations	No case – fatty liver	No case
9	No case (heart failure-related, γ GT elevated, slightly high AP, ALT <2 × ULN)	No	Yes	Yes	Requested and received	No case – minor elevations probably due to CHF	No case – long-term minor elevations	No case
10	No case (jaundice, cholestasis, pseudocyst of pancreas)	No	No	No	Not requested	NA	NA	NA
11	No case (AP <2 × ULN, no alternative cause, ALT and BIL normal)	No	No	No	Not requested	NA	NA	NA

γ GT = γ-glutamyltransferase; **AP** = alkaline phosphatase; **BIL** = direct bilirubin; **CHF** = congestive heart failure; **NA** = not assessed; **PCP** = primary-care practitioner; **ULN** = upper limit of the normal range.

case of acute liver disorder. Details of the review process by which acute liver disorder cases were assessed are given in table I.

The total time taken for this study, from the target period through to final review, was 18 months. Of this time, 6 months was the target observation period, and the remaining 12 months were accounted for by data logistics and management, and case validation. Based on the number of patients recruited in this study, the time span required to achieve the target number of 15 000 new users would be 11 and 16 months for amoxicillin/clavulanic acid and low-dose aspirin, respectively. Thus, it would have been necessary to extend the target observation period by a factor of 2–3 times in order to detect or rule out a signal of relevance to public health. For the purposes of our feasibility analysis, it was decided not to pursue such an extension.

The speed at which the current method will detect pharmacovigilance signals is dependent upon both the rate of market uptake for a drug and the incidence of the adverse event. The uptake of six new medicinal products commonly used in primary healthcare is shown in figure 4. The data revealed that the target exposure of 15 000 individuals for each new drug would not be reached before the fifth year of marketing in a single database. Taking into account these figures, we constructed different real-world scenarios to estimate the follow-up time needed to generate relevant signals (table II).

Discussion

Principal Findings

The current pilot study aimed to achieve a proactive surveillance of drug-associated acute liver disorder within a period of 18 months (6 months patient accrual plus 12 months data logistics and management). During this time, the target population was identified, potential case assignments were made using computerized records, and final case assessments were achieved using paper-based medical information from potential cases. Based on the actual number of patient-years accrued, it was determined that a study period closer to 30 months (18 months patient accrual plus 12 months data logistics

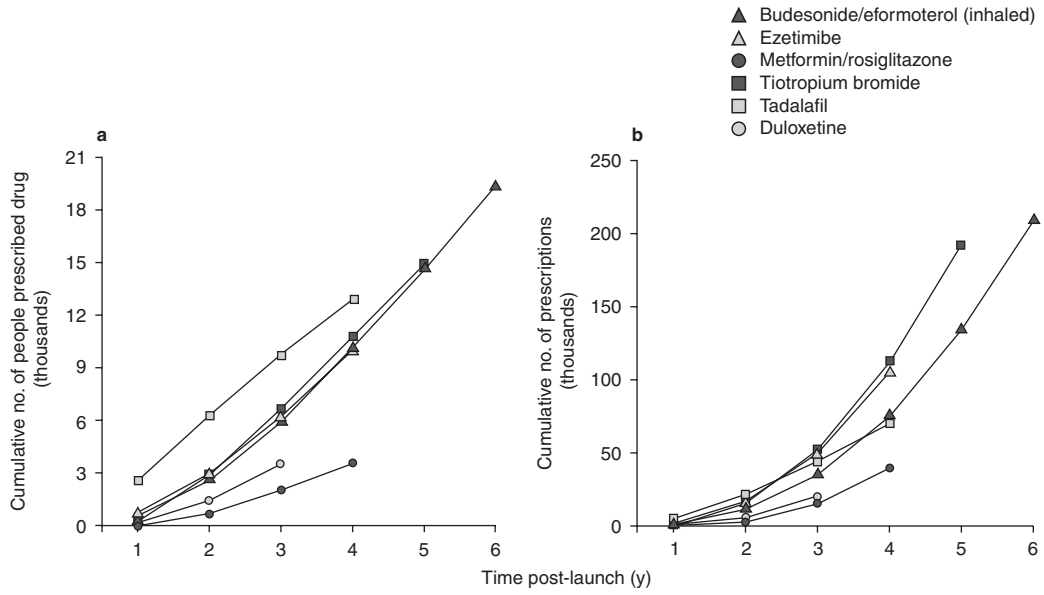

Fig. 4. Cumulative number of people prescribed (**a**) and cumulative number of prescriptions (**b**) for six commonly used drugs launched between 2001 and 2006 in the UK.

Table II. Estimated follow-up required in a single general practice database to detect new adverse drug effect signals under different scenarios

Incidence of the adverse drug reaction	Required target exposure[a]	Estimated follow-up period required (y)			
		very high uptake >10 000[b]	high uptake 6000–10 000[b]	medium uptake 3000–6000[b]	low uptake <3000[b]
1 in 1000 new users	3 000 new users	<0.3	0.5–0.3	1–0.5	>1
1 in 5000 new users	15 000 new users	<1.5	2.5–1.5	5–2.5	>5
1 in 10 000 new users	30 000 new users	<3	5–3	10–5	>10

a Minimum sample size required to detect with 95% confidence at least one adverse reaction occurring at the given incidence.

b Average number of new users per year in a database containing information of about 3 million people.

and management) would have been required to adequately detect or rule out a signal of drug safety.

In performing this surveillance, we have demonstrated the logistical feasibility of using an independent endpoint adjudication committee to identify potential adverse events, using immediately accessible data from a healthcare database. However, we have also shown that for events with a frequency of 1 in 5000 or less, a single database may fall short and multi-site studies should be considered for most new drugs.

Strengths of the Study

Although clinical trials represent the gold standard for assessing drug efficacy, their capacity to predict the safety profile of a drug once released on to the market is limited. Traditionally, post-launch drug safety monitoring has been carried out using information obtained from spontaneous reporting. Pharmacoepidemiological methods that use historical data from healthcare databases or information from field-based studies have complemented these methods by allowing more accurate quantification of drug safety signals.

This study aimed to complement existing drug surveillance methods by testing the feasibility of using a healthcare database, the GPRD, in combination with an independent endpoint adjudication committee, to monitor the safety of a therapeutic product proactively. This approach can be guided by information on potential safety issues identified either during the developmental phase, or from theoretical risks based on a compound's mode of action, and would be particularly useful for the development of pharmacovigilance risk management plans.[18]

Another strength of this system is the impartial nature of the data produced. By using an existing model of data collection, which does not interfere with normal working practices within the healthcare environment, collection bias is probably much reduced. The geographically representative nature of the GPRD also means that external validity is achieved. In terms of impartiality, the current process was made open and transparent by allowing staff at the GPRD in London to administer the data query. This transparency extended to the board of external experts (who may include staff from regulatory authorities, and independent clinical experts) who are able to review cases without the involvement of contracting parties, thus improving data credibility.

Limitations of the Study and Future Directions

One of the limitations demonstrated by the present study was the difficulty in identifying sufficient patient numbers to generate a signal concerning low-frequency adverse events. Based on our analysis, even the largest available database may not be sufficient to detect (within a reasonable timeframe) an adverse event affecting not more than 1 per 5000 people. However, this limitation could be overcome by regularly querying multiple databases. Other systems within Europe that would be suitable for this purpose include THIN in the UK, the Database for Pharmacoepidemiological Research in Primary Care (BIFAP) project in Spain, which contains information on approximately 2 million

patients, or the Integrated Primary Care Information project in the Netherlands, which is expected to cover over 1 million patients within the next few years. Although the characteristics of these healthcare databases may vary considerably, it should be possible to apply similar standardized definitions on exposure and outcome measurements. Furthermore, potential cases identified from multiple databases could be evaluated by the same board of experts. Crucially, the specific makeup of the endpoint adjudicating committee should reflect the adverse event(s) under investigation, so that sufficient specialist knowledge is available to make accurate final case assessments.

In this study, we did not assess an adverse event associated with the launch of a new drug. Rather, we sought to mimic this situation by studying patients who were newly prescribed drugs already established in the market. In future, implementation of this study design will require parameters to be optimized depending on the properties of the drug being launched. In that respect, one could expect to be able to reduce the 12-month period required for the data management and case ascertainment. These parameters include the target study population, inclusion/exclusion criteria, threshold for signal generation, and the type of data used. For example, this study excluded individuals with a record of acute liver disorder before the target period. In a real-world scenario, individuals with a previous history of a disease may be the most vulnerable to a specific adverse drug reaction and would therefore need to be included. This study also did not use free-text comments because the number of computer cases was small enough that chart abstraction was feasible for all of them. In other situations, this resource may be essential for improving the efficiency of the study. Finally, because we did not find an acute liver disorder signal in this feasibility study, we were unable to validate the signal using nested case-control analyses (after adjusting for potential confounders) or to confirm the signal using another database.

Despite the availability of some suitable automated healthcare databases, overall there is a paucity of such systems. The methodology described here requires large-volume databases that include prescription data and are regularly updated with patient information. Individual (rather than aggregate) data must be available and must include well documented information on demographics, diagnoses, outcomes and medicinal exposures. The available follow-up time for a study population must be sufficient to answer the research question and correctly classify comorbidities and treatment history. Similarly, original medical records should normally be accessible for validation of potential outcomes in most studies. These prerequisites limit the usefulness of some claims- and record-linkage data sources that have considerable delays in follow-up times, and in the provision of morbidity/mortality outcome data. Hence, the further development and international harmonization of primary-care databases and registries should be strongly encouraged.

Conclusions

We have demonstrated the feasibility of setting up an active drug safety monitoring system using a public healthcare database in combination with an independent endpoint adjudication committee. This method, in combination with spontaneous reporting, prescription event monitoring and other pharmacoepidemiological methods, has the potential to further enhance the speed at which drug safety signals can be accurately detected and quantified.

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endpoint adjudication committee received a fee for participating in this study.

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References

1. Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the Food and Drug Administration, 1998-2005. Arch Intern Med 2007; 167 (16): 1752-9
2. Strom BL. Pharmacoepidemiology. 4th ed. London: John Wiley & Sons, 2005
3. De Abajo FJ. Improving pharmacovigilance beyond spontaneous reporting. Int J Pharmaceut Med 2005; 19 (4): 209-18
4. Waller PC, Evans SJ. A model for the future conduct of pharmacovigilance. Pharmacoepidemiol Drug Saf 2003; 12 (1): 17-29
5. European Commission: Enterprise and Industry. Rules governing medicinal products in the European Union: guidelines on pharmacovigilance for medicinal products for human use [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol9_en.htm [Accessed 2009 Dec 21]
6. European Commission: Innovative Medicines Initiative. The Innovative Medicines Initiative (IMI) strategic research agenda: creating biomedical R&D leadership for Europe to benefit patients and society [online]. Available from URL: http://imi.europa.eu/docs/imi-gb-006v215022008-research-agenda_en.pdf [Accessed 2009 Dec 21]
7. Institute of Medicine of the National Academies. The future of drug safety. promoting and protecting the health of the public. Washington, DC: The National Academies Press, 2007
8. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. BMJ 1991; 302 (6779): 766-8
9. García Rodríguez LA, Pérez Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. Br J Clin Pharmacol 1998; 45 (5): 419-25
10. Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. Pharmacotherapy 2003; 23 (5): 686-9
11. Hollowell J. The General Practice Research Database: quality of morbidity data. Popul Trends 1997; Spring (87): 36-40
12. Lucena MI, Garcia-Cortes M, Cueto R, et al. Assessment of drug-induced liver injury in clinical practice. Fundam Clin Pharmacol 2008; 22 (2): 141-58
13. Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol 1990; 11 (2): 272-6
14. Garcia Rodriguez LA, Stricker BH, Zimmerman HJ. Risk of acute liver injury associated with the combination of amoxicillin and clavulanic acid. Arch Intern Med 1996; 156 (12): 1327-32
15. De Abajo FJ, Montero D, Madurga M, et al. Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br J Clin Pharmacol 2004; 58 (1): 71-80
16. García Rodríguez LA, Ruigómez A, Jick H. A review of epidemiologic research on drug-induced acute liver injury using the general practice research data base in the United Kingdom. Pharmacotherapy 1997; 17 (4): 721-8
17. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. JAMA 1983; 249 (13): 1743-5
18. Cooper AJ, Lettis S, Chapman CL, et al. Developing tools for the safety specification in risk management plans: lessons learned from a pilot project. Pharmacoepidemiol Drug Saf 2008; 17 (5): 445-54

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