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SEMI-AUTOMATED IDENTIFICATION OF POTENTIAL ADVERSE DRUG EVENTS

Plößnig M[1], Schuler J[2], Hansbauer B[3], Stroka S[1], Engel T[4], Hofer-Dückelmann C[5], Radulescu M[1], Adlassnig K-P[4, 6]

Abstract

The amount of drugs used in medical care leads to an increased risks of Adverse Drug Events (ADEs). With the iMedication project we aim at identifying ADEs in hospitals at an early stage, through the use of triggers. The paper presents the classification of such triggers and the distributed knowledge sources supporting trigger checks. The assessment of ADEs and the collaborative reporting process for reviewing suspicious ADEs are described.

Keywords – medication, adverse drug event, trigger, medical expert system

1. Introduction

Drug treatment is connected with growing costs. In 2009, drug expenditures in Germany were at about 30.5 billion Euro with an increase of 2.2 billion Euro for drugs in 2009 [7]. Studies in Britain and USA have shown that there are more deaths from adverse drug events (ADEs) than from traffic deaths [5]. In Britain, up to 56.000 hospital beds are occupied annually by patients admitted with ADEs accounting for 4% of the hospital bed capacity [11]. A UK study examining 18.820 hospitalisations identified 1225 ADEs as primary reason for the hospital treatment (representing 6,5% of all hospitalisations). 70% of the hospitalisations with drug effects were assessed to be avoidable and 28 patients died in consequence of the ADEs [11]. Despite a legal commitment to report each ADE health care professionals reported only 3823 cases to the Austrian authorities in the last 5 years [1]. This relevant underreporting challenges the principle of pharmavigilance itself and great efforts have to be undertaken to improve this incidental reporting system.

1. 1. Patient Safety and Electronic Medication

Patient safety deals with the reporting, analysis, and prevention of medication errors that often lead to ADEs. The reasons for adverse events are manifold and can be traced back to human factors (e.g.

[1] Salzburg Research Forschungsgesellschaft, Salzburg

[2] Gemeinnützige Salzburger Landeskliniken Betriebsgesellschaft mbH, Salzburg

[3] Paracelsus Medical University, Salzburg

[4] Medexter Healthcare, Vienna

[5] Landesapotheke am St. Johanns-Spital, Salzburg

[6] Medical University of Vienna, Vienna

time pressures, fatigue), complex medical situations (e.g. complicated technologies, complex drug interactions, comorbidities) or system failures (e.g. poor communication). Prevention of medication errors is currently a growing field of importance for patient safety. Drug therapy is an integral part of medical treatment and there are many possible causes for an ADE, e.g. intrinsic danger of drugs (adverse drug reactions) and medications errors (wrong dosage, interactions, transcription errors based on unreadable prescriptions, ignoring allergies, etc.) [4]. Most ADEs occur in hospitals or two weeks after discharge. 50% of all ADEs are considered as preventable [2].

In recent years medication safety has become a primary concern in many national healthcare systems and hospitals. Information technology is regarded as having a great potential to help improve safety standards in healthcare. Electronic healthcare records and Computerized Physician Order Entry (CPOE) systems are already supporting prescriptions and automated medication. CPOE systems are adopted to reduce medication errors by supporting physicians in prescription situations with checks (e.g. drug interactions, allergies) and recommendations (e.g. dosage calculation, alternative medication suggestions), ideally based on individual patient data [10]. The majority of these systems is proprietary and offers little integration with other knowledge sources. Even exchange with Hospital Information Systems remains limited. Since there is no proof, that CPOE systems really reduces ADEs, there is a need for more research and development in this field [12].

Looking at European research projects one priority is to develop systems that can monitor and analyse adverse events. EU-ADR[7] used ICT technologies for demonstrating new ways to exploit the existing clinical and biomedical data sources for the early detection of Adverse Drug Reactions. Special attention was given to children and other patient groups who typically are not involved in clinical trials. The project PSIP[8] deals with ADEs due to product safety problems and medication errors due to human factors. PSIP identified ADEs in hospital by involving patient records.

1. 2. Discovering and Categorizing Adverse Drug Events

Traditional efforts to detect Adverse Drug Events (ADEs) have been based on voluntary reporting and tracking of errors. However the majority of ADEs remains undiscovered. At the most 30% of prescription errors cause a clinical event, 70% remain undetected [2]. A more effective method for measuring the level of harm from medications in a health care organization is the use of so-called "triggers". Usually, the methodology is a retrospective review of a random sample of in-patient hospital records using triggers to identify possible adverse events. Often this process is supported by a trigger tool which includes a list of known ADE triggers (like gastrointestinal bleeding, falls, confusion, electrolyte imbalances, etc.) and instructions for identifying ADEs. An identified trigger indicates only the presence of an trigger, but not necessarily an adverse event. A detailed examination is needed in order to determine whether an adverse event has actually occurred [6].

Using ADE monitors can help to support the review process electronically. Previous studies (e.g. [6]) have demonstrated the use of ADE detection monitors to identify suspicious ADEs. Seger [14] for example describes a computerized ADE monitor using electronic medical records from outpatient practices. The ADE monitor uses rules derived from coded medication names and laboratory results, text-based rules based on clinicians' notes and symptoms linked to

[7] EU-ADR "Early detection of adverse drug events by integrative mining of clinical records and biomedical knowledge" http://www.alert-project.org/

[8] PSIP "Patient Safety through Intelligent Procedures in Medication" http://www.psip-project.eu/

medication.One result of the study shows that triggers are sometimes context-related, e.g. triggers which are useful in an in-patient setting did not yield valid results in an ambulatory setting.

2. iMedication – Identifying Suspicious Adverse Drug Events

The iMedication[9] project aims at developing an intelligent ADE cockpit for monitoring, assessing and reporting ADEs based on a medical expert system supporting the early identification of ADEs. The basic approach for the ADE risk identification are triggers which are clues for possible ADEs. A trigger is based on patient data in combination with the current medication. The decision whether a trigger indicates an ADE is specified by rules written in Arden Syntax[10]. Depending on the results of the ADE check the attending physician or a clinical pharmacist will be informed. If there is a serious suspicion of an ADE it will be evaluated and classified by a review team of at least two medical specialists. If the ADE suspicion is confirmed then iMedication will support the reporting process to the competent authority which collects ADEs for a country (the AGES[11] for Austria).

2. 1. Distributed Knowledge Sources

Information and hints for ADEs are distributed over multiple sources. A primary source in iMedication is the electronic health record (EHR) that potentially reveals hints for ADEs. Patient data are either imported from the Hospital Information System (HIS) or if not available they are integrated semi-automatically. Currently, iMedication considers patient data such as master patient data, lab results, information about findings, symptoms, diagnoses, medication and risk factors. Additionally, iMedication makes a contribution towards linking data in the eHealth domain by connecting distributed data silos on the Web. Essential knowledge sources for iMedication are information about drugs (in particular the Summary of Product Characteristics), about drug interactions and articles about ADEs including existing problems and precautions related to medication. Some of these sources are available on the Internet such as the arznei-telegramm[12], a German journal publishing articles about drugs and reported risks, information about approved drugs for Austria[13] or UptoDate Lexi-Comp[14], an American interaction database.

Finally, iMedication takes a step towards administrating medical knowledge and data via semantic web technologies. ADEs and their relations to the patients and their medication is a central concept of the semantic model in iMedication. Resource Description Framework (RDF)[15] is used as a format for structuring and representing these data. Whenever applicable medical standards and taxonomies are used such as LOINC[16] for laboratory observations, SNOMED[17] for classifying symptoms and risk factors, ICD-10[18] for assigning diagnoses and ATC[19] for classifying drugs. iMedication uses SKOS[20] for representing these medical taxonomies.

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10 http://www.hl7.org/implement/standards/ardensyntax.cfm

11 http://www.ages.at/

12 http://www.arznei-telegramm.de

13 http://pharmaweb.ages.at/pharma_web/index.jsf

14 http://www.uptodate.com/contents/drug-interaction

15 http://www.w3.org/RDF/

16 LOINC - Logical Observation Identifiers Names and Codes, http://loinc.org/

17 SNOMED - Systematized Nomenclature of Medicine, http://www.ihtsdo.org/snomed-ct/

18 ICD - International Statistical Classification of Diseases, http://www.who.int/classifications/icd/en/

2. 2. ADE Trigger

ADEs can be detected in many different ways. iMedication chose the approach of Morimoto et al. which proved to be suitable for the detection of ADEs by means of different patients' characteristics [8]. In their paper the authors describe a method to detect ADEs by the combination of the patients' medication with data from laboratory results, symptoms, diagnoses, and additional sources:

- *Medication – Drug interaction:* combining two or more drugs can affect the activity of drugs by pharmacological interactions between the drugs. These drug-drug-interactions can lead to increased or reduced efficacy and adverse events. They can also result in new side effects that neither drug would produce on its own.
- *Medication – Symptom:* a single symptom can be a first indication of an underlying ADE, e.g. dry cough with ACE-inhibitors. Other symptoms like nausea are less specific and are difficult to assign to a medication. The detection and documentation of symptoms in a hospital setting is rarely systematic and often there are only handwritten notes from physicians and nurses in the patient chart. Thus iMedication will provide a catalogue of symptoms allowing the implementation of this source.
- *Medication – Diagnosis:* diagnoses can serve as triggers in detecting and preventing ADEs. The diagnosis bradycardia for example can be a hint for an overdosing of ß-Blockers. Certain drugs are contraindicated in patients with a specific diagnosis (e.g. ß-Blockers in patients with asthma bronchiale).
- *Medication – Laboratory:* laboratory values are typical and easy to use triggers for the detection of ADEs. Many drugs can lead to specific changes of laboratory values. Abnormal laboratory values can be the result of organ damage caused by drugs, but not all deviating laboratory values are associated with organ damage. Abnormal laboratory results can go along with clinical symptoms. To determine the actual concentration of substances in the body they can be measured in body fluids. This allows therapeutic drug and the detection of overdosing.

Each trigger is assigned by an ADE risk score value represented by an integer between 1 and 3 (1 = low ADE risk, 3 = high ADE risk) based on literature and expert opinions. Based on all detected triggers and their risk score values for a suspicious ADE an ADE-Risk-Score is calculated. The ADE-Risk-Score indicates the severity of this suspicious ADE. If iMedication reports suspicious ADEs the result basically includes the ADE-Risk-Score, the detected trigger, recommendations for the clinician and an explanation component with the relevant patient data. The ADE-Risk-Score goes from 1 = minimal risk to 5 = high risk and subsumes the individual ADE risk values of the detected triggers. Depending on the measured severity, responsible persons will be informed. These persons can either be the treating physician in the hospital and / or the clinical pharmacist responsible for assessing and reporting of ADEs.

2. 3. Collaborative Reporting Process

If the ADE-Risk-Score indicates the suspicion of a severe ADE (ADE-Risk-Score ≥ 4) then the plausibility check and the ADE classification will be executed by a review team. Typically, the review team consists of two specialists (e.g. a clinical pharmacist and a physician specialized in

[19] ATC – Anatomical Therapeutic Chemical, http://www.whocc.no/atc/structure_and_principles/

[20] SKOS - Simple Knowledge Organization System, http://www.w3.org/2004/02/skos/

medication safety) evaluating the ADE suspicion independently from each other [5]. The ADE review and reporting process comprises the following steps:

1) *Plausibility check* – one of the reviewers evaluates whether the ADE suspicion is an adverse drug reaction and whether the ADE reporting process should be proceeded. In many cases, the assessment is based on personal expertise. iMedication supports this step by providing relevant information from the distributed knowledge sources about drugs, drug interactions and reported ADEs.
2) *Classification of the ADE* – if the result of the plausibility check advises to continue with the ADE assessment the two reviewers will be working independently supported and guided by the iMedication workflow. The reviewers have to decide on the causality between the drug therapy and the ADE based on the six WHO causality categories [15]. They classify the suspicious ADE according to the 10 point Naranjo adverse reaction probability scale [9] and assess the quality, severity, preventability and the accordance with the ICD-classification for ADEs.
3) *Comparison of the review results* – based on the review results the reviewers decide whether the suspicious ADE is unlikely to be caused by the drugs involved or whether the ADE should be reported to the AGES.

3. Discussion and Outlook

In 2012, iMedication will be evaluated in a hospital setting at the Salzburg University Hospital (Salzburger Landeskliniken). The project consortium decided to focus on four use cases which are typical clinical situations with an inherent risk for ADEs – hyperkalemia, hyponatremia, renal failure and overanticoagulation. These cases cover the most frequent ADEs in the internal medicine [13] and therefore the triggers, rules and test scenarios in iMedication are created around them. They can be seen as a first training set for iMedication evaluated in selected wards. For a comprehensive adoption of iMedication in a clinical setting the number of triggers and rules has to be expanded. Additionally, ADEs assessed and approved by the review team will be stored in the ADE knowledge base. A forthcoming task will be to analyse whether meaningful additional triggers can be identified from the ADE knowledge base, e.g. based on statistical methods. It is expected that these triggers may point out additional risk patterns for the four use cases.

Typically, ICT applications in hospitals including HIS have evolved organically and in the past, hospitals developed their own medical taxonomies and standards. Hence, adopting established medical taxonomies and interoperability standards is an ongoing but slow process and iMedication aims at importing standard-based data as much as possible but also offering the possibility to complete patient data semi-automatically. Nevertheless, with the health expert's expectations of future electronic medication as integrated part of the EHR interoperability and integration issues are of growing importance. Patient data might not only be included from the HIS but also from additional sources e.g. from general practitioners or the patients themselves. Interoperability standards medical taxonomies for classifying patient data are prerequisites in this process.

iMedication represents a novel development route for increasing medication safety. It is not necessarily combined with the prescription step. It can be used retrospectively, e.g. comparing with some past time frame for statistical or quality reasons or for identifying patients with an ADE risk, e.g. on a daily basis. iMedication can be integrated into the HIS and invoked every time patient data representing a trigger (e.g. lab results or medication) are updated. Thus, iMedication represents an intelligent ADE cockpit for the monitoring and assessing of possible ADEs.

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Corresponding Author
Manuela Plößnig
Knowledge and Media Technologies, Salzburg Research Forschungsgesellschaft
Jakob Haringer Straße 5/III, A-5020 Salzburg
Email: manuela.ploessnig@salzburgresearch.at