Adverse Drug Event Monitoring with Clinical and Laboratory Data Using Arden Syntax

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Abstract

In times of steadily increasing numbers of administered drugs, the detection of adverse drug events (ADEs) is an important aspect of improving patient safety. At present only about 1–13% of detected ADEs are reported. Raising the number of reported ADEs will result in greater and more efficient support of pharmacovigilance. Potential ADE's must be identified early. In the iMedication system, which is a rule-based application, triggers are used for computerized detection of possible ADEs. Creating a pilot system, we defined the relevant use cases hyperkalemia, hyponatremia, renal failure, and over-anticoagulation; knowledge bases were implemented in Arden Syntax for each use case. The objective of these knowledge bases is to interpret patient-specific clinical data and generate notifications based on a calculated ADE risk score, which may indicate possible ADEs. This will permit appropriate monitoring of potential ADE situations over time in the interest of patient care, quality assurance, and pharmacovigilance.

Keywords:

Drug Related Side Effects and Adverse Reactions; Drug Monitoring; Decision Support Systems, Clinical.

Introduction

Medical errors or unintentional acts of omission or commission, or those that do not achieve their intended outcome [1] – such as inappropriate medication – do occur in hospitals. A recent study stated that medical errors are the third leading cause of death in the U.S. [2], making it more important than ever to prevent and mitigate medical errors, especially those causing damage to patients [3].

The fact that drugs are being administered in increasing numbers signifies a greater potential for drug-related harm, including adverse drug events (ADEs). Traditionally ADEs are tracked and reported on a voluntary basis. Hence the success of ambulatory error reporting systems has been limited; approximately 10–20% of medication errors and only 1–13% of detected ADEs are reported [4]. Additionally, the process of ADE detection consumes considerable resources in terms of time and money. Studies have shown that as many as 6% of all hospital admissions are due to ADEs, and this number is three-fold higher among elderly patients [5, 6]. Moreover, about 50% of these prescribing errors and ADEs are deemed avoidable [7]. Hospitals need a more efficient mode of quantifying the degree and severity of ADEs, such as automated or computerized detection. Identification of severe ADEs as well as measuring their frequency will enable pharmacists and physicians to take corrective measures.

iMedication supports the process of pharmacovigilance – the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, especially the long-term and short-term side effects of medication [8] – by identifying potential ADEs. Using automated tools such as iMedication, it is possible to reduce the number and severity of ADEs over time, identifying potential ADEs as early as possible, supporting plausibility checks on suspected ADEs, and reporting verified ADEs in an appropriate and standardized manner. Furthermore, it can inspire physicians and pharmacists to report ADEs and – last but not least – save time and money during the reporting process.

Existing approaches for computerized ADE detection employ methods such as data mining [9] and decision trees [10] to automatically generate ADE detection rules. Another strategy is to utilize the rich semantics of ontologies such as SNOMED CT [11, 12], and apply it to the detection of ADEs via semantic querying and reasoning. Others approach the task by the automatic creation of rules with the aid of product label parsing [13]. In the iMedication project, we integrate the operative knowledge of local and remote experts by linking distributed knowledge repositories, and manually derive specific rules from expert knowledge. This enables us to specify complex rules for the identification of ADEs. The system reports detected ADEs according to their severity. The reports additionally include an explanation as to how the knowledge base came to its conclusion to report an ADE. Furthermore, the report provides information that helps the physician or clinical pharmacist to take corrective therapeutic measures. If necessary, a report is forwarded to the Austrian Agency for Health and Food Safety (AGES), the agency responsible for pharmacovigilance in Austria. The workflow of ADE identification, verification, and reporting is shown in Figure 1.

In the present paper we report the results of a pilot study on effectiveness performed in 2012. Using data on patients admitted to the University Hospital of Salzburg (UHS) in 2007 and 2011, we analyze the sensitivity and specificity of the system in detail.

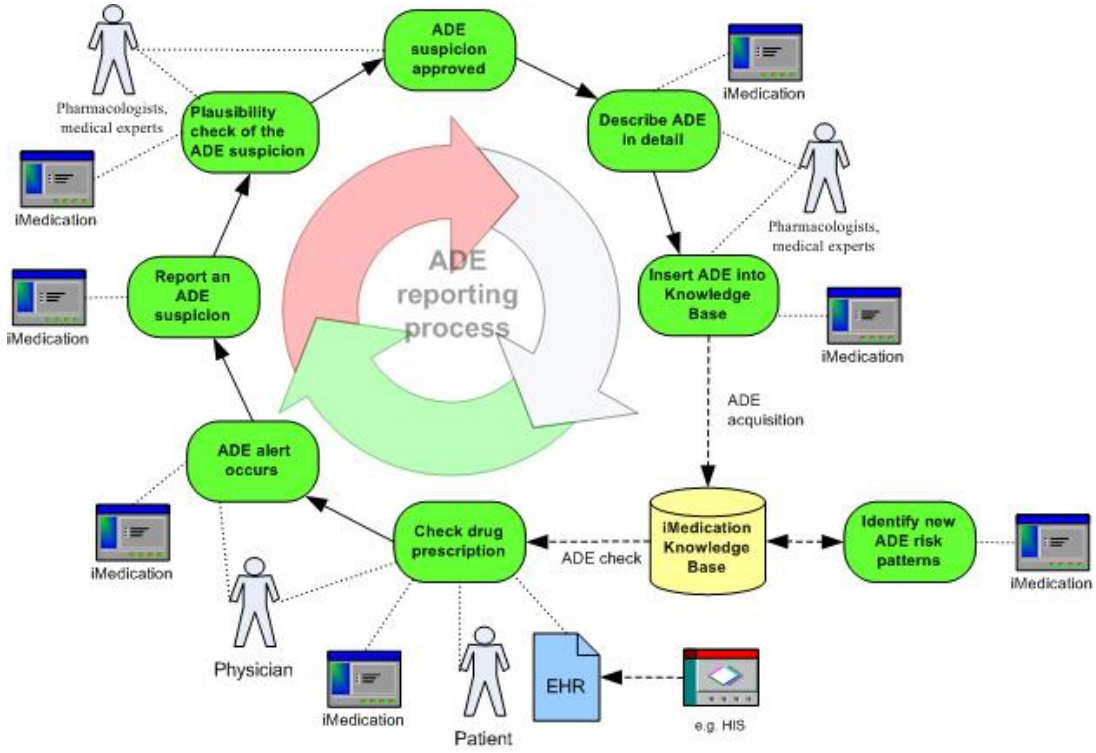

Figure 1 – Workflow of adverse drug event (ADE) detection and reporting.

Methods

Theoretical foundations

The iMedication system is founded on the principles of the "Institute for Healthcare Improvement (IHI) Global Trigger Tool" method [3] and Morimoto's classification [14] for the detection of possible ADEs.

The IHI Global Trigger Tool for Measuring Adverse Events is a method of identifying adverse events – especially those causing harm – and measuring the rate of adverse events over time. The method employs *triggers* – clues on possible adverse events – to track adverse events, including ADEs. However, the tool is not meant to identify all adverse events, but rather performs a retrospective review of a random sample of inpatient data [3].

According to Morimoto et al. [14], irregular use of medication (referred to as incidents) can be classified in many ways: actual ADEs vs. potential; preventable vs. non-preventable; ameliorable vs. non-ameliorable; and errors vs. non-error. According to this method, an ADE is regarded as an injury due to medication.

In general, incidents are identified by collecting practice data, soliciting incident reports from patient caregivers, and surveying patients directly. These data are then independently reviewed by patient caregivers using various triggers, such as:

- Symptoms or actions that suggest a (potential) ADE or medication error, such as a new rash or new diarrhea.
- Diagnoses associated with (potential) ADEs or medication errors, such as poisoning by drugs.
- The use of specific drugs that suggest an ADE may have occurred.
- Drug combinations known to cause ADEs or the use of duplicate drugs.
- Combinations of drugs and symptoms that might indicate a (harmful) reaction to the drug, such as diarrhea or eruption due to antibiotics.
- Combinations of drugs and patient diagnoses, such as bleeding and antiplatelet agents or warfarin.
- Combinations of drugs and other factors such as patient age or sex, or pregnancy.
- Laboratory triggers, such as microbiology results that show improper use of antibiotics.

Study design, setting, and participants

We conducted a retrospective single-center cohort study on sample data that were collected prospectively and validated. The study was performed at UHS, a tertiary-care and teaching hospital. In this study we focused on two key groups in ADE detection: women and the elderly. Data from the UHS were collected from patients admitted in 2007 or 2011 to any ward of the Department of Internal Medicine (I+II). All female adult patients (age $\geq$ 18 years) admitted for at least 24 hours were eligible for the study. An additional age constraint was imposed on patients admitted in 2007: all of them had to be older than 75 years.

Data management and sample size

Demographic patient information as well as clinical and laboratory values were obtained through systematic interrogation and sampling of the hospital information system (HIS). A total of 70 patient cases were selected for the study; 22 from 2007 and 48 from 2011.

Data sources

Patient data were collected from various sources, such as the UHS's HIS, or manually entered data. The following six main categories were used:

- *Demographic data* including demographic information such as age, sex, weight, height, pregnancy, or epidemiological studies.
- *Laboratory findings* provided by the HIS, such as serum creatinine, potassium, sodium, etc. Different time frames exist for absolute and relative findings. Absolute values are only taken into account within a time frame of three days prior to the data of calculation, whereas relative values permit a time frame of seven days.
- *Symptoms* that occurred during the preceding seven days are integrated into the analysis.
- *Diagnoses* are defined according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). A single diagnosis is identified by a 3- to 7-digit code (such as E87.5 for hyperkalemia). When more than one diagnosis from a diagnostic group is detected in the patient's chart, all of the diagnoses from this group are counted as a single trigger.
- *Medications* are specified by the Anatomical Therapeutic Chemical Classification System (ATC), according to which a single substance is defined by a 7-digit code.
- *Hospital events* denote any consultations of psychiatrists or trauma surgeons and internal accident reports during the hospital stay.

Risk score calculation

Risk score values and rules were determined by clinical and pharmacological experts and are assigned to ADE triggers which are processed by an algorithm to calculate an overall ADE risk score on a given scale (1–5). Based on the ADE risk score, appropriate reminders are sent to the physicians and pharmacists. Furthermore, reporting forms are prepopulated with the relevant patient data and the suspicion of an ADE.

The ADE risk score calculation consists of five main steps:

1. Patient data filtering. Only those data elements within a specified timeframe related to the calculation date and specified conditions are relevant for the calculation process. The time frames are based on clinical experience. Patient data shall be integrated when the medication that may cause an ADE has been administered during the preceding three days.
2. The recognition of at least one medication which may cause the possible ADE is a prerequisite for the calculation of an ADE risk score and the specific rules.
3. Depending on the number of positive triggers from each category, a contribution to the ADE risk score is calculated. The maximum value over all categories is added to the ADE risk score (see Table 1).
4. The ADE risk score is adapted by a value that depends on the quantity of the patient's medication (see Table 2).
5. Standardization of the last ADE risk score is the last calculation step. The maximum value for the ADE risk score is 5.

Table 1. The adverse drug event risk score increases, depending on the number of positive triggers

For each category
1–2 triggers with an ADE risk score of 1: increase value by 1
≥3 triggers with an ADE risk score of 1: increase value by 2
≥1 trigger with an ADE risk score of 2: increase value by 2
≥1 trigger with an ADE risk score of 3: increase value by 3
new ADE risk score = old ADE risk score + (maximum of categories increase values)

Note: ADE, adverse drug event.

Table 2. The adverse drug event score increases, depending on the number of administered medications

The occurrence of 2–4 different medications from the medication lists causing the ADE for the use case results in an increase of the ADE risk score by 1.
The occurrence of >4 different medications from the medication lists causing the ADE for the use case results in an increase of the ADE risk score by 2.

Note: ADE, adverse drug event.

Knowledge base and data processing

Four highly critical clinical situations, namely hyperkalemia, hyponatremia, renal failure, and over-anticoagulation, were defined as use cases for the iMedication project. These constitute significant ADEs in internal and geriatric medicine. The four knowledge bases in iMedication are based on these use cases, which are implemented in Arden Syntax, which is a knowledge representation and processing language supported by HL7 International [15]. Each knowledge base consists of several medical logic modules (MLMs) [16, 17], which are the basic knowledge representation and processing units in Arden Syntax and are executed by an Arden Syntax engine [18]. In all there are 33 MLMs, taking 51 ADE triggers into account.

Data are processed as follows: First, all relevant data are collected and aggregated into an information block – a patient object – and forwarded to the Arden Syntax server. The Arden Syntax engine processes the obtained information and returns one result object for each knowledge base and each day. The return objects contain complete patient data, thus permitting the explanation and tracing of decisions made by the iMedication system. Also, for each category the fired triggers are stored and attached. The result object includes information on the severity of the detected ADE; this information determines the ADE risk score.

Presentation of results

We use patient demographic information (age, length of stay, number of verified ADEs) and treatment information (number of administered medications) to describe the patient population. We also discuss the number and risk score of ADE triggers during the study period. We define each ADE trigger with a risk score ≥ 4 as a "positive test", and ADEs with lower risk scores as a "negative test". Using this classification, we determine the effectiveness of the system as well as its sensitivity (SEN), specificity (SPE), positive predictive value (PPV) and negative predictive value (NPV) metrics.

Results

The mean age of the patients was 76.5 years (standard deviation 13.3 years, minimum 43 years, maximum 99 years). The mean duration of the hospital stay was 11.2 days (standard deviation 10 days, minimum 2 days, maximum 53 days). On average, a patient received 8.5 medications during his/her stay (standard deviation 4.7; minimum 1 medication, maximum 29 medications).

Of the 70 patients included in the study, 16 (22.8%) experienced one or several ADEs confirmed by patient caregivers. Twelve patients with ADEs were registered in the study population of 2007, and 4 patients with ADEs among those examined in 2011. In all 26 ADEs were confirmed for the four medical situations implemented in the knowledge base: 2 for hyperkalemia, 13 for hyponatremia, 8 for renal failure, and 3 for over-anticoagulation.

A total of 428 triggers were generated during the study period. An overview of these triggers and their scores are shown in Table 3.

Table 3. Number of triggers generated during the study period and their associated scores.

Trigger score	**Frequency**
Score 0	306
Score 1	9
Score 2	9
Score 3	34
Score 4	34
Score ≥ 5	36
Total	**428**

Using the previously mentioned classification for a “positive test” and a “negative test”, we constructed a 2x2 contingency table (Table 4). Based on the absolute numbers in the contingency table, the system showed a SEN of 85%, a SPE of 88%, a PPV of 31%, and a NPV of 99%.

Table 4. 2x2 Contingency table for the study results

	ADE confirmed	**ADE absent**	**Total**
Positive test	22	48	**70**
Negative test	4	354	**358**
Total	**26**	**402**	**428**

Note: ADE, adverse drug event.

Discussion

We present the iMedication system, a computerized system that supports pharmacovigilance by detecting and reporting potential ADEs. We outlined the underlying principles and mechanics of the system, and established the sensitivity and specificity of the current pilot system. However, it needs to be refined before it can qualify as a trustworthy alarming system (PPV 31%).

Computerized trigger tools for inpatient ADEs perform moderately well, are inexpensive to use, and already deployed in many hospitals [19]. The iMedication system was able to correctly identify 85% of all ADEs, which is many times higher than the numbers of commonly reported ADEs (1–13%) [4]. According to a recent study, only 4.5–5.5% of ADEs are reported in Austria [21].

The iMedication system is able to help clinicians in many ways. First, a retrospective evaluation of clinical data permits quality assurance through statistical analysis of detected potential ADEs. Second, physicians are given active feedback (notifications) during the treatment of their patients, thus enabling them to take corrective measures in a timely manner. Finally, the iMedication system supports (semi-)automated ADE reporting by notifications to the pharmacist with prepopulated forms. As a result, ADEs can be avoided or corrected. When they do occur, their reporting consumes less resources.

The limitations of the study are worthy of mention. First, in the present evaluation phase, data input is accomplished semi-automatically because all relevant patient data are not available in electronic form. Furthermore, the four use cases currently implemented in the knowledge base need to be evaluated in a wider setting and improved in order to avoid alert fatigue. Finally, additional studies will be carried out to evaluate the iMedication phenomenon of much more frequent ADE reports to the AGES than is achieved by conventional reporting.

Conclusion

We showed that a comprehensive solution for the (semi-) automated detection and reporting of ADEs is not only feasible but also effective. Given the fact that the tracking and reporting of ADEs occur on a voluntary basis, the integration of an automated computerized method in clinical routine would provide more information about the scope of the ADE problem at a minimal expense of resources.

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