Evaluation of automated term groupings for detecting upper gastrointestinal bleeding signals for drugs

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Abstract. Studies in pharmacovigilance suggest that statistical detection of new signals should take into account several terms related to a medical concept rather than a single preferred term. We built an OWL-DL file with formal definitions of MedDRA and SNOMED-CT concepts and performed two queries, Query 1 and 2, to retrieve MedDRA terms within the ‘Upper Gastrointestinal bleeding’ safety topic. The EB05 metric (from MGPS statistical test) is measured for 50 active ingredients randomly selected in the FDA pharmacovigilance database for both queries and the safety topic. Coefficient of determination was $R^2 = 0.87$ between Query 1 and the safety topic; $R^2 = 0.99$ between Query 2 and the safety topic. Automated groupings of terms for upper gastrointestinal bleeding generates similar values in signal detection compared to our gold standard. We are currently improving the modeling of MedDRA terms in order to increase precision and recall for other safety topics.

Keywords. Pharmacovigilance, MedDRA, SNOMED-CT, Ontology, Signal detection

Introduction

The continuous development of new drugs requires an early detection of their unknown adverse effects [1]. Case reports are usually coded with the MedDRA\textsuperscript{®} terminology [2] (Medical Dictionary for Drug Regulatory Activities) and stored in databases that constitute putative knowledge on suspected adverse drug reactions (ADRs). MedDRA is a terminology used by regulatory authorities and the biopharmaceutical industry to code information in ADR reports [3]. Standardized MedDRA Queries (SMQ) are groupings of MedDRA terms, that relate to a defined medical condition or area of interest and which are intended to support case identification [4]. However they do not cover all medical conditions that may be related to a drug or may not have the required specificity. For example a SMQ is currently available for ‘gastrointestinal bleeding’ but not for ‘upper gastrointestinal bleeding’. MedDRA users may ask the MSSO for the addition of new SMQs in MedDRA. SMQs are constructed manually by expert consensus and can be reused as a standard to allow international comparison between drugs. Our objective is to implement methods in order to support the generation of new SMQs in an automated way by proposing a list of candidate terms according to the description of a safety topic where the user may choose the most relevant terms.

We assume that it is possible to generate groups of MedDRA terms using knowledge engineering methods to represent a given clinical condition [5]. A prerequisite to perform such groups by terminological reasoning (logical inferences based on semantic content) is that formal representations of the terms are available [6].

\textsuperscript{1} MedDRA\textsuperscript{®} is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations
To that aim, we have developed an OWL-DL (Web Ontology Language – Description Logic) file with formal definitions of ADRs: OntoADR [7] in order to support semantic query-based generation of groups of terms relating to similar medical conditions.

Several authors have studied the impact of grouping terms before signal detection with different outcomes [10-11]. The goal of the present study is to compare results of a data mining algorithm for statistical research of signals in pharmacovigilance databases between the SMQ and our DL-query based MedDRA terms grouping method. We performed this evaluation on the US Food and Drug Administration’s (FDA) public database [12]. This study reports results about a single safety topic: ‘Upper gastrointestinal bleeding’.

I. Methods

1.1 OntoADR

OntoADR² [7] (November 2011 build was used in this study) is an OWL-DL file with formal definitions of adverse drug reactions that is being developed to support logic queries and to perform terminological reasoning for MedDRA terms groupings. Concepts are defined with semantic properties corresponding to relations used in the medical domain as defined in SNOMED-CT® (Systematized Nomenclature of Medicine – Clinical Terms) clinical terminology. Twenty-six relations were selected among which: hasFindingSite, which specifies the body site affected by a condition; or hasAssociatedMorphology, which describes the morphologic changes seen at the tissue or cellular level that are characteristic features of a disease.

To define MedDRA concepts in OntoADR, we used UMLS (Unified Medical Language System) metathesaurus to extract mappings between MedDRA and SNOMED-CT. OntoADR was extended by adding semantic properties of a SNOMED-CT concept C_Sno to a MedDRA concept C_Med when they were synonymous within UMLS. For example, ‘Gastric haemorrhage’_Med is mapped with ‘Gastric hemorrhage’_Sno which is semantically defined with hasAssociatedMorphology ‘Hemorrhage’ and hasFindingSite ‘Stomach structure’.

Two queries were developed to match the safety topic: ‘Upper Gastrointestinal bleeding’. The first one, named Query 1, is a basic query targeting hemorrhage in the upper gastrointestinal tract structure.

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hasFindingSite some 'Upper gastrointestinal tract structure'
AND hasAssociatedMorphology some 'Hemorrhage'

(Query 1)
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Query 2 aims to add investigations and findings related to gastrointestinal bleedings.

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hasFindingSite some 'Upper gastrointestinal tract structure'
AND hasAssociatedMorphology some 'Hemorrhage'

OR

interprets some 'Occult blood screening'
AND hasInterpretation some 'Positive'

OR

interprets some 'Evaluation of stool specimen'
AND hasAssociatedMorphology some 'Hemorrhage'

(Query 2)
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² Access to OntoADR is currently not public due to license requirements related to MedDRA® and SNOMED-CT®.
1.2 Signal Detection

Multiple statistical tests are used to identify signals of ADRs that are significantly reported more frequently than expected. We selected MGPS (Multi-item Gamma Poisson Shrinker) because it is recommended by the FDA [13].

Input data for this study were taken from the public release of the FDA’s Adverse Event Reporting System (AERS) database, covering the period from the first quarter of 2004 to the end of 2010. Prior to analysis, all adverse events were converted to MedDRA Preferred Terms (PTs) and all drug names coded with free text were cleaned-up using text mining approach. Duplicate reports and follow-ups were also deleted in order to keep the most recent case number (a numerical id describing a case report in FDA AERS database). We randomly selected 50 active ingredients from the 500 most frequent drugs present in FDA case reports. We used MedDRA version 14.1 in English Language [13]. As term grouping reference (gold standard) for our topic ‘Upper Gastrointestinal bleeding’ we manually selected terms from ‘SMQ Gastrointestinal hemorrhage’ related to the upper part of the gastrointestinal tract (27 PTs out of 50 terms). A formal definition was achieved manually by knowledge engineers and pharmacovigilance experts when no mapping was available in UMLS for a MedDRA term within this selection.

For every couple {active ingredient, group of terms} we calculated EB05 (a disproportionality measure for MGPS) values. We compared theses values between each group of terms (SMQ selection for our Safety topic, Query 1 and Query 2). To evaluate the proportion of variability in the values, we used the coefficient of determination $R^2$, which is the correlation coefficient squared. We estimated if there was a linear relation ($y = ax + b$) or even equality ($y = x$) between signal values for SMQ and our groupings. The coefficient of determination $R^2$ ranges from 0 to 1, giving some information about the goodness of fit of a model, an $R^2$ of 1.0 indicates that the regression line perfectly fits the data.

2. Result

The content of Query 1 and SMQ selected terms for our safety topic was similar:

$\text{Recall} = \frac{\text{relevant terms \cap retrieved terms}}{\text{total relevant terms}} = 74.1\%, \text{Precision} = \frac{\text{relevant terms \cap retrieved terms}}{\text{retrieved terms}} = 83.3\%$

Seven preferred terms present in SMQ were absent from Query 1 but 5 of them (‘Gastric occult blood positive’, ‘Haematochezia’, ‘Melaena’, ‘Melaena neonatal’, and ‘Occult blood positive’) where caught in Query 2 (Recall: 92.6%, Precision: 86.2%). The remaining terms absent from Query 2 were ‘Duodenal operation’ and ‘Ulcer haemorrhage’. In the same time both queries proposed 4 additional preferred terms (‘Aorto-oesophageal fistula’, ‘Erosive duodenitis’, ‘Gastric antral vascular ectasia’ and ‘Portal hypertensive gastropathy’).
Figure 1. EB05 values for Query 1 (left) and 2 (right) vs. SMQ selected terms

Figure 1 illustrates how statistical values for signal detection are correlated between each query grouping and the SMQ terms used as gold standard. Each dot represents a couple {active ingredient, group of terms} (x and y coordinate are EB05 values). EB05 measures with query groupings and the SMQ grouping are highly correlated. This linear relationship is indicative that low (respectively high) measures of EB05 using the safety topic are related to low (respectively high) measures of EB05 when using our groupings.

3. Discussion

MedDRA terms returned by Query 2 are similar to the safety topic’s content taken as gold standard. This result confirms the hypothesis that the modeling of MedDRA terms through methods of knowledge engineering and DL-queries allows to automatically generate lists of terms comparable to manually grouped terms in this terminology.

Two MedDRA terms related to the upper part of the digestive tract (‘Duodenal operation’ and ‘Ulcer hemorrhage’) were not retrieved by our queries. First, ‘Duodenal operation’ which is present in the reference SMQ, refers to a procedure possibly related to upper gastrointestinal bleeding treatment. It is possible to design a query in order to catch such procedures, but, it would return all terms directed to this anatomical location and generates a lot of noise (about 50 new terms). The relevancy of those supplementary terms related to procedures in the grouping has to be discussed. Second, ‘Ulcer haemorrhage’ can’t be caught with the query because it is not semantically defined as a gastro-intestinal related ulcer in MedDRA. It belongs to the ‘Haemorrhages NEC’ group, which implies that, strictly speaking, it refers to ulcer haemorrhages that can be located in other parts in the body.

Four additional terms were retrieved by both query 1 and 2. ‘Erosive duodenitis’ is candidate for addition in the ‘Gastrointestinal haemorrhage’ SMQ because it describes a disorder with the inflamed duodenal wall. Other terms are not a priori related to drugs. ‘Aorto-esophageal fistula’ occurs in a setting of prior aortic reconstructive procedures or in pathology of aorta. The etiology and pathogenesis of ‘Gastric antral vascular ectasia’ are still not known. ‘Portal hypertensive gastropathy’ refers to changes in the mucosa of the stomach in patients with portal hypertension.
The use of OWL-DL queries by pharmacovigilance professionals seems impractical. This is why we are currently developing a user interface to facilitate queries and selection of terms. Our study focuses on a single safety topic, but we already replicated similar results on ‘Anaphylactic Shock’ and ‘Neutropenia’ topics and we plan to make such analysis on other safety topics. This will allow us to evaluate how groupings can improve signal detection. In a future work we will study the impact of using single preferred terms, existing MedDRA groupings and our novel groupings by plotting the evolution of EB05 values over time. This will allow us to compare whether single preferred terms or groups of preferred terms help to catch signals earlier.

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References