Original Article

Developing a signal triage algorithm for Thai national adverse drug reaction database

Chootima Jamekornkul[1], **Suntharee T. Chaisumritchoke**[2]

[1]Health Product Vigilance Center, Food and Drug Administration, Nonthaburi, Thailand, [2]Department of Social and Administrative Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand

ABSTRACT

There has been increasing adverse drug reaction (ADR) reports submitted to the Health Product Vigilance Center under the Thai Food and Drug Administration. To find some signals, the Thai Signal Detection Program was developed to identify and filter the potential signals, called signals of disproportionate reporting (SDRs). A large number of SDRs cannot be in-depth assessed by the Signal Detection Advisory Working Group (SDAWG) in time. The prioritized SDRs with concentrated in-depth assessment might help in finding some true signals. This preliminary study aimed at developing a signal triage algorithm that can prioritize SDRs to assign an in-depth assessment for true signals and to test the proposed triage algorithm and compare against the traditional method by the SDAWG. Multi-criteria decision analysis was chosen for proposing a triage algorithm by generating scores for priority rankings of the clinical importance of SDRs. This study had three main steps. Key attributes for a triage decision were first identified and followed by the development of a signal triage algorithm. After that, the triage algorithm was tested by comparing the triage results of the proposed algorithm with triaging by experts in the SDAWG. Six factors were selected as key attributes, i.e., fatal outcome, serious ADRs, positive rechallenge, new drug, change in number of ADR reports, and source of reports. Four attributes used in the Thai Signal Detection Program were excluded, i.e., the drug-ADR associations, WHO-ART critical term, disproportionality, and volume of reports. Six experts gave the weight for the six key attributes using their experiences, and score criteria were set. To test the proposed triage algorithm, systemic antibiotics with 86 SDRs in total were triaged by the SDAWG, and eight SDRs were chosen for further assessment. Six of them were consistent with the result of the proposed signal triage algorithm (75% agreement) and were the top of the priority ranking. The other two SDRs were selected only by the SDAWG because they were high-concerned and serious ADRs and unfamiliar cases. These could be because of the drug or ADRs of current interest, the level of being key attributes, comorbidity and concurrent medication use, and characteristics of experts' opinions. The signal triage algorithm can enhance the efficiency of the triage method by experts as it is systematic, transparent, timely, repeatable, and also scientifically based. More research is necessary to evaluate and/or improve this triage algorithm.

Corresponding Author:
Suntharee T. Chaisumritchoke, Department of Social and Administrative Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Phyathai Road, Pathumwan, Bangkok, 10330, Thailand.
Tel.: +662-218-8330, Fax: +662-218-8336, E-mail: suntharee.t@chula.ac.th

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INTRODUCTION

The principal concern of pharmacovigilance system is the timely signal detection [1]. In the early stage of pharmacovigilance, reports of adverse drug reaction (ADR) were assessed case-by-case by experts or expert groups for signals. As the number of ADR reports has been continuously increasing, it has made the traditional method hard to keep up. Computer-assisted tools using data mining algorithms (DMAs) by applying the statistical value of the proportional reporting ratio (PRR), reporting odds ratio (ROR), Bayesian confidence propagation neural network (BCPNN), or multi-item Gamma-Poisson Shrinker which were developed for systematic signal detection at an aggregated level. Signals from DMAs are specifically called signals of disproportionate reporting (SDRs) [1].

However, it is often found that DMAs offer a large number of SDRs, and any further in-depth investigation of all SDRs is time-consuming and less likely to be possible. In

addition, not all SDRs are of high medical importance because some are false positive or false negative. The signal triage algorithm has consequently been developed to prioritize SDRs or potential signals to focus on those that actually require significant actions which would be, for example, to confirm true signals, to prove the association, or to issue risk minimization actions [2,3].

In Thailand, the Health Product Vigilance Center (HPVC) under the Food and Drug Administration (FDA) works as the national pharmacovigilance center. It is responsible for safety surveillance of health products and ADR reporting system. Each year, more than 30,000 ADR reports are submitted to the Thai-FDA. So far, there are more than 450,000 reports in the Thai Vigibase [4]. To help in detecting possible signals, the HPVC had developed a DMA, called the Thai Signal Detection Program, by applying the ADR, ROR and filter criteria such as number of reports, quality of reports, being a WHO critical term etc., to limit the number of SDRs.

Each year up to 10,000 primary potential signals or SDRs were generated by the Thai Signal Detection Program. Due to the limitations of time and experts in the HPVC, the Signal Detection Advisory Working Group (SDAWG) was assigned to be in charge with the signal detection process of SDRs, and the Clinical Evaluation Advisory Working Group was designated to confirm the true signals. 10,000 primary potential signals were prioritized and assessed by the HPVC and the working groups using their expertise and experience. Only some drug groups and a few primary potential signals were chosen for in-depth assessment for true signals.

This is a preliminary study to develop an automatic triage algorithm to assist the traditional triaging by experts in the SDAWG by offering a systematic, timely, and scientifically based algorithm and to test the proposed triage algorithm and compare against the traditional method by the SDAWG. More research is necessary to evaluate and/or improve this triage algorithm.

METHODS

This study used the multi-criteria decision analysis (MCDA) concept to propose a signal triage algorithm because it was described as a transparent and explicit decision-making process dealing with many criteria or attributes by weights and scores. The signal triage decision was determined by the clinical importance of drug-ADR associations, based on the number of reports containing such drug-ADR associations, being new associations, serious reactions, or fatal outcome.

This study was carried out in 3 main steps. First, the key attributes to the triage decision were identified. Second, the signal triage algorithm was developed by selecting and weighing the key attributes and setting the score procedure. The signal triage decision was based on clinical importance scores which were derived based on attribute weights and attribute scores. Third, the proposed triage algorithm was tested by comparing the triage result of the proposed algorithm with triaging by experts.

RESULTS

Identification of Key Attributes of the Triage Decision

Attributes of drug-ADR associations that had inherited higher clinical importance were collected, prioritized, and assigned to work in the triage algorithm [5-8]. First, the potential attributes to triage decision were collected from the literature review. Second, they were grouped according to their characteristics. Finally, the key attributes were applied in the proposed signal triage algorithm.

PubMed (http://www.ncbi.nlm.nih.gov/pubmed) was used for finding literatures related to signal triage decision. Using keywords “signal detection,” “signal selection,” “prioritize signal,” and “triage ADR” from 1999 to 2012 and quick reading for their correlation to the triage process, 225 papers were identified to explore more detailed information about characteristic of attributes.

The 14 attributes to the triage process from literature review were collected and classified according to their characteristics into 3 dimensions as follows:

- ADR character: New drug-ADR association, WHO-ART critical term, fatal outcome, serious ADR, positive dechallenge, positive rechallenge, preventive measures, biological plausibility, or drug class effect
- Drug character: New drug
- ADR measures: Disproportionate reporting, volume of reports, change in number of ADR reports, number of sources of reports, and types of reporters.

Among the collected attributes that affected the triage decision, some attributes did not have enough power to differentiate the importance of drug-ADR associations in Thai ADR database, i.e., positive dechallenge and reporters because very few reports were dechallenge and more than 98% of reporters were pharmacists. Some attributes could not be obtained from ADR report or retrieved from the database, i.e., biological plausibility and preventive measures. Furthermore, four attributes had already been used in the Thai Signal Detection Program, i.e., drug-ADR associations, WHO-ART critical term, disproportionality, and volume of reports. Therefore, the above-mentioned attributes were not regarded as key attributes.

Six attributes were chosen as the key attributes to develop the proposed triage algorithm which was fatal outcome, serious ADRs, positive rechallenge, new drug, change in number of ADR reports, and sources of reports.

Development of the Signal Triage Algorithm

In this stage, six experts were required to weight the relative importance of each attribute to the triage decision. The experts from the SDAWG were involved in this process. They were 3 experts from the academic sector including pharmacists and toxicologists, one expert from Thai-FDA and one from the HPVC. The experts must be members of the SDAWG and had actively participated in the working group meeting because most of the triage processes at the national level in Thailand were performed by the SDAWG.

The questionnaire was constructed to solicit the opinions of the experts about weights that reflect the importance of the key attributes in the triage method. It requested their judgment by rating 0-4 scale (1-not important, 2-not very important, 3-important, and 4-very important). Most of the experts rated the serious case as very important attribute (average score = 3.8), followed by fatal outcome case (3.4), new drug (3.2), and positive rechallenge case (2.4), respectively. The least important among the key attributes were new report (2.2) and multiple sources of reports (2.2).

The average score of the level of importance was transferred to relative importance weight used in the triage algorithm. The results were 22% for serious case, 20% for fatal outcome, 14% for positive rechallenge, 18% for new drug, 13% for change in number of ADR reports, and 13% for multiple sources of reports. After incorporating the weighted attributes, the scoring procedure was set, and then the triage algorithm was already to be used (Figure 1).

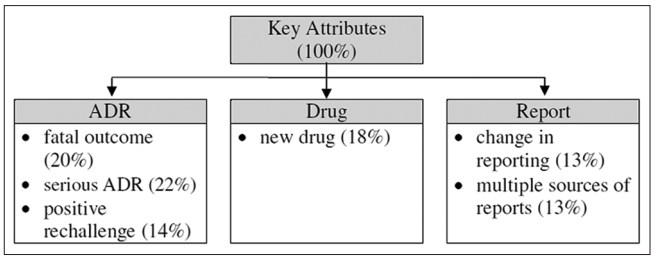

Figure 1: Weighing of key attributes

Comparing the Result of the Triage Algorithm with the Collective Judgment from the SDAWG

To test the model, we choose the systemic antibiotics to be tested since they were recently prioritized for in-depth investigation for true signals. Two methods such as triaging by the proposed triage algorithm and by collective judgment from the SDAWG were compared for the effectiveness of the methods in the following aspects.

Input

Time, human resource or experts, and expenditure were the main input of the triage method. It was clearly seen that time and human resources used in the triaging method by the proposed triage algorithm were less than the collective decision by the SDAWG. The time used in preparing the input data of two methods is nearly the same since it included time used in retrieving the data from the database and preparing the input documents. In the past events, the SDAWG took about 1 h and around ten experts to assess and prioritize 86 SDRs (0.116 man-h/SDR) to get some SDRs for further in-depth assessment, compared to <15 min with one technician (0.003 man-h/SDR) using the proposed triage algorithm. Expenditure of the SDAWG is also higher than the proposed triage algorithm since the SDAWG covers about ten experts' travel cost, but the proposed triage algorithm covers one technician's cost. Some experts in the SDAWG have travel expense by air to join the meeting.

Process

The triage process begins with assessing the SDRs and assigning of priority order to be further assessed for true signals on the basis of clinical importance. The effectiveness of the triage process can be explained by being systematic, transparent, timely, repeatable, and scientifically based approach. The triage judgment processes in the SDAWG were dealing with opinions and experiences which sometimes were more complex and involved more bias than triaging by the triage algorithm. In this study, the proposed triage algorithm used MCDA, and the priority was the ranking of the clinical important scores of SDRs which are clear and easy to explain. The proposed triage algorithm is also easy-to-use, easy-to-understand, and can be adjusted to cope with new situations. Apart from this, it is a quantitative and repeatable method.

Output

The prioritized SDRs were the output of triage process. The systemic antibiotics with a total of 86 SDRs (by Thai Signal Detection Program) were triaged by the SDAWG in the meeting on 21 September 2012 [9]. The SDAWG agreed to select eight SDRs to be further assessed. Six of them were consistent with the result of the proposed signal triage algorithm (75% agreement), and they were on the top of the priority ranking. The other two SDRs selected only by the SDAWG were acute renal failure associated with imipenem + cilastatin in which the SDAWG had seen it as a high concern, serious ADR and convulsions associated with cefpirome which the SDAWG had seen it as an unfamiliar case (Table 1).

DISCUSSION

This study used MCDA such as the triage algorithm proposed by Levitan *et al*. (2008). In this study, the proposed triage algorithm targeted to prioritize the SDRs in the large scale of national database with the weak point of additional data cannot be obtained from the old ADR reports and the input data as they existed in the database. Levitan *et al*. applied more attributes and specified only the unconfounded and unexpected ADRs in some drug classes. Some attributes need more medical judgment such as drug class effect, which could not be obtained directly from the ADR report. Another triage algorithm was proposed by Waller *et al*., (2005) using impact analysis. They prioritized SDRs into four groups (A = high priority - detailed evaluation needed; B = there is a need to gather more information; C = low priority, but still needs to be addressed; D = no action warranted at the present time) considering the same attributes as other studies. Some attributes required further medical judgment such as the scoring of non-fatal outcome. Some attributes were difficult to find data such as the reporting rate since drug utilization data of particular drugs such as over-the-counter drugs are hard to find.

There were some differences between the results of triaging SDRs in systemic antibiotics by the proposed triage algorithm and the collective judgment from the SDAWG which can be explained as follows.

Drug/ADRs in Current Interest

Some ADRs are of high concern in public health since they are serious ADRs and can be fatal outcome to the patient. There

Table 1: The triaged SDRs in systemic antibiotics prioritized by the proposed signal triage algorithm and by the SDAWG

SDRs		Triaged by	
Drug	**ADR**	**Triage algorithm**	**The SDAWG**
Streptomycin	Epidermal necrolysis	✓	✓
Streptomycin	Stevens–Johnson syndrome	✓	✓
Sulbactam+cefoperazone sodium	Dermatitis exfoliative	✓	✓
Tetracycline	Epidermal necrolysis	✓	✓
Streptomycin	Hepatitis	✓	✓
Tetracycline	Stevens–Johnson syndrome	✓	✓
Roxithromycin	Angioedema	✓	-
Tetracycline	Erythema multiforme	✓	-
Imipenem+cilastatin	Acute renal failure	-	✓
Cefpirome	Convulsions	-	✓

"✓" indicated that the SDR was selected for further assessment. SDAWG: Signal detection advisory working group, ADR: Adverse drug reaction

were totally 86 SDRs (by Thai Signal Detection Program) for systematic antibiotics. The SDAWG had prioritized eight SDRs of which six SDRs were consistent with the triage algorithm (75% agreement). The inconsistencies were acute renal failure associated with imipenem + cilastatin because the SDAWG had seen it as a high concern, serious ADR and convulsions associated with cefpirome, which the SDAWG had seen it as an unfamiliar case. Other drug groups with various drugs and ADRs should be tested for the effectiveness of the proposed triaged algorithm.

Key Attributes

The proposed triage algorithm had used all of the six pre-set key attributes that were serious cases, fatal outcome, new drugs, positive rechallenge cases, changing in number of ADR reports, and multiple sources of reports. The proposed model used two levels of the key attributes (with or without the attribute which was considered as serious or non-serious), but the SDAWG considered more levels of the attributes with their own experiences. For example, they see the difference of serious levels of generalized edema and heart failure which are both in the same level of "serious ADRs" as identified by the WHO. That can explain one cause of disagreement of the triage results. The relative important weights and rankings can be developed empirically and modified on the basis of experiences (such as adding some more levels of the key attributes) to suit the situation of drug surveillance.

Comorbidity and Concurrent Medication Use

In patients taking systemic antibiotics, they had some tendencies to have comorbidity with other disease and/or concurrent medication use of drugs that were involved in concerned ADRs. They can increase the false positive or false negative case from the triage process.

Experts

A decision which depends on the experiences and knowledge of experts or expert groups can deal with bias, especially when they are from different backgrounds and have different experiences and interests. Another observation is that there are also some differences in their awareness of special drugs or ADRs. Some experts concern more about new drugs whereas others concern about drugs use in public health programs. Furthermore, the decision was sometimes qualitative, sometimes subjective and not repeatable since the composition of the group of experts could be changed or some interests had changed.

The differences between the results of triaging SDRs by the proposed triage algorithm and the collective judgment from the SDAWG indicated that there was the human ability that cannot be replaced by machines or algorithms. They can concern about other attributes besides those in the proposed triage algorithm. All of the SDRs chosen by the proposed triage algorithm or the SDAWG should be reconsidered whether they require further assessment.

The signal triage algorithm will maximize its performance if the SDRs and ADR reports as the input of the algorithm are of high quality. The quality of some ADR reports was not very good. Although all of them were completely filled with four essential elements (source of reports, patient identification, drug, and ADRs), some elements did not correlate with others. The quality of ADR reports should be promoted to all kinds of reporters. Other than this, encouraging ADR reporters to add more data such as attached documents can be helpful. Improving the DMA by considering other statistical values such as PRR, BCPNN instead of ROR, and adjusting for other criteria to obtain the SDRs can increase the effectiveness of the signal triage method and signal detection process.

The proposed triage algorithm can be used to support the effectiveness of the collective judgment by the SDAWG by shortening the time used in screening data and fulfill the justification of the SDAWG to be systematic, transparent, repeatable, and also scientifically based along with the SDAWG that providing the human ability to justify what the triage algorithm cannot done.

The further study should consider the necessity to add the attributes that cannot be obtained from ADR reports or retrieved from the database, i.e., biological plausibility or drug class effects, preventive measures, and special interest.

In some situations, only some drug groups need some specific data. The additional database will be provided to serve this particular group.

CONCLUSION

The proposed triage algorithm in this preliminary study can be used to assist the experts in the triage decision since it is a scientific, systematic, transparent, and repeatable method. In proposing the triage algorithm, all key attributes should be considered, weighed, and ranked according to the supported technical documents and experts' knowledge. The proposed triage algorithm should be tested with various input data to assure the effectiveness of the algorithm.

The key attributes, their weights, and scores applied in the triage algorithm should be periodically adjusted to fit the public health situation which can change over time. Some drug groups have specific factors influencing the importance to triage decision, particularly drug groups which are used more in comorbid patients and concurrent medication uses such as anti-inflammatory and antirheumatic products. Consideration of modifying the triage algorithm to serve these types of drugs such as adding more levels of the key attributes will support the effectiveness of the triage algorithm.

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