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

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Objectives: There was increasing adverse drug reaction (ADR) reports submitted to the Health Product Vigilance Center under the Thai FDA. 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 find some true signals. This preliminary study aimed at developing a signal triage algorithm that can prioritize SDRs to assign an in-depth assessment.
Methods: A multi-criteria decision analysis (MCDA) was chosen for a triage algorithm by generating scores for priority rankings on clinical importance of SDRs. This study had three main steps. Key attributes for a triage decision was 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.
Results: Six factors were selected as key attributes, i.e. fatal outcome, serious ADRs, positive rechallenge, new drug, change in reporting and sources 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. Experts gave the weight for the six key attributes using their experiences. To test the proposed algorithm, systemic antibiotics with 86 SDRs in total were triaged by SDAWG and eight SDRs were further assessed. Six SDRs were consistent with the result of the proposed signal triage algorithm (75% agreement) that was the top of the priority ranking. The other two SDRs were selected by SDAWG because of the highly-concerned, serious ADR and unfamiliar case. These could be because of the drug or ADRs for the current interest, level of key attributes, comorbidity and concurrent medication use, and characteristics of experts' opinions.
Conclusion: 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.

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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 made the traditional method hard to achieve. Computer-assisted tools using data mining technique with data mining algorithms (DMAs), 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. Additionally, not all SDRs are of high medical importance; some are false positive or false negative. Signal triage has consequently been developed to prioritize signals of disproportionate reporting (SDRs) or potential signals in order 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 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 Thai Vigibase.[4] In order to detect possible signals, HVPC has developed a data mining algorithm (DMA), called Thai Signal Detection Program, by applying the ADR reporting odds ratio (ROR) and filter criteria such as number of reports, quality of reports, being a WHO critical term etc. in order to limit the number of SDRs. The Signal Detection Advisory Working Group (SDAWG) was assigned to be in charge with signal detection process and the Clinical Evaluation Advisory

Working Group (CEAWG) to confirm for true signals. Up to 1,000 drug-ADR associations were presented as primary potential signals. Only some associations were in-depth assessed for true signals. This is a preliminary study to develop an automatic triage algorithm to assist the traditional triage by experts.

Methods

This study used multi-criteria decision analysis (MCDA) concept to propose a triage algorithm. The signal triage decision depends on the clinical importance of drug-ADR associations by generating numeric scores for rankings of priority. This study is carried out in 3 main steps. First, identify the key attributes to the triage decision. Second, development of the signal triage algorithm, and the triage criteria were selected and weighted by the experts. Third, test the proposed triage algorithm by comparing the triage result of the proposed algorithm with triaging by experts.

Results

1) Identification of Key Attributes to the Triage Decision

Attribution of drug-ADR associations that have inherited higher clinical importance were collected, prioritized and assigned to work in the triage algorithm.[5-8] Firstly, the potential attributes to triage decision were collected from the literature review. Secondly, they were grouped according to their characteristics. Lastly, the key attributes were selected to be applied in the proposed signal triage algorithm.

The collected key attributes to the triage process were classified according to their characteristics into 3 dimensions as follows:

- ADR: 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: new drug.
- ADR Report: disproportionate reporting, volume of reports, change in reporting, number of sources of reports, reporters

Among 14 attributes that affected the triage decision, some attributes those did not have enough power to differentiate the importance of drug-ADR associations i.e., positive dechallenge and reporters. Some attributes could not be obtained from ADR report or retrieved from the database i.e., biological plausibility, and preventive measures. Four attributes have been used in the Thai Signal Detection Program i.e., drug-ADR associations, WHO-ART critical term, disproportionality and volume of reports. Six attributes were selected as the key attributes to propose the triage algorithm which were fatal outcome, serious ADRs, positive rechallenge, new drug, and change in reporting and sources of reports.

2) **Development of the Signal Triage Algorithm**

In this stage, six experts were required to weight the relative importance of each attribute to triage decision. The experts from SDAWG were involved in this process. They were 3 experts from the academic sector including pharmacists and toxicologists, one expert from Thai Food and Drug Administration and one from HPVC.

The questionnaire was constructed to solicit the opinion of the experts about weights that reflect the importance of the key attributes in the triage method. It requested their judgment by rating 0 to 4 scale. The ratings of the level of importance were transferred to relative importance weight used in the triage algorithm. The results are 22% for serious case, 20% for fatal outcome, 14% for positive re-challenge, 18% for new drug, and 13% for change in reporting and for multiple sources of reports each. After incorporating the weighted attributes and scoring procedure, the triage algorithm was already to be used.

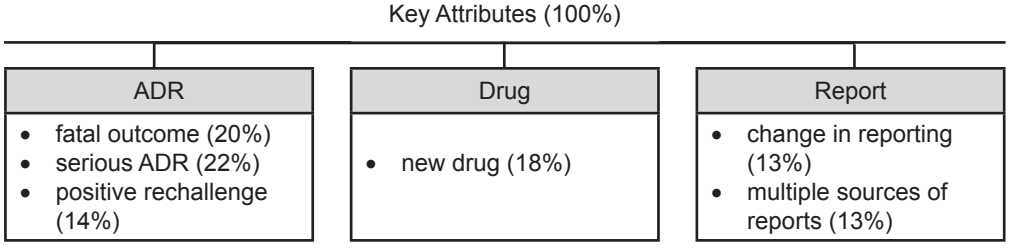

Figure 1: Triage algorithm model: weighting of key attributes.

3) **Comparing the result of the triage algorithm with the collective judgment from SDAWG.** To test the model, we choose the systemic antibiotics to be the testers since they were recently prioritized to in-depth investigation for true signals. Two methods - triaging by the proposed triage algorithm and by collective judgment from SDAWG - were compared in the following aspects:

- **Input:** 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 SDAWG. SDAWG took about 30 minutes and around 10 to 12 experts to select 4 from 11 drug-ADR associations. Some experts have travel expense for traveling by air to join the meeting.

- **Process:** The triage judgement processes in the SDAWG were more complex and involved more bias than triaging by the triage algorithm. In this study, the MCDA was used and the priority was the ranking of the important scores of SDRs. It is 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 systemic antibiotics with totally 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 8 SDRs to be further assessed. Six SDRs were consistent with the result of the proposed signal triage algorithm (75% agreement) since they were on the top of the priority ranking. The other 2 SDRs selected by SDAWG was acute renal failure associated with imipenem + cilastatin in which SDAWG had seen it as a high-concern serious ADR and convulsions associated with cefpirome which SDAWG had seen it as an unfamiliar case.

Table 2: The triaged SDRs in systemic antibiotics prioritized by the proposed signal triage algorithm and by SDAWG.

NO	SDRs		Triaged by	
	Drug	AE	triage algorithm	SDAWG
1	streptomycin	epidermal necrolysis	✓	✓
2	streptomycin	Stevens Johnson syndrome	✓	✓
3	sulbactam+cefoperazone sodium	dermatitis exfoliative	✓	✓
4	tetracycline	epidermal necrolysis	✓	✓
5	streptomycin	hepatitis	✓	✓
6	tetracycline	Stevens Johnson syndrome	✓	✓
7	roxithromycin	angioedema	✓	-
8	tetracycline	erythema multiforme	✓	-
9	imipenem + cilastatin	renal failure acute	-	✓
10	cefpirome	convulsions	-	✓

"✓" indicated that the SDR was selected for further assessment.

Discussion

There are some differences between results of triaging SDRs in systemic antibiotics by the proposed triage algorithm and the collective judgment from 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 were totally 86 SDRs (by Thai Signal Detection Program) in systematic antibiotics. The SDAWG had prioritized 8 SDRs of which 6 SDRs were consistent with the triage algorithm (75% agreement). The inconsistencies were acute renal failure associated with imipenem + cilastatin because SDAWG had seen it as a high-concern serious ADR and convulsions associated with cefpirome which 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 6 pre-set key attributes that were serious cases, fatal outcome, new drugs, positive re-challenge cases, changing in reporting and multiple sources of reports which covered almost all of the important attributes for triaging. The proposed model used the level of with or without the attributes (such as serious/non-serious) but SDAWG considered more level of attributes with their own experiences. For example, they see the different serious levels of generalized oedema and heart failure which are the serious ADRs as identified by 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 the sublevel) 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 can involve in concerned ADRs. They can increase the false positive or false negative of the triage process.

Experts: A decision which depends on the experiences and knowledge of experts such as expert groups can deal with bias especially when they are from different backgrounds and have different experiences. Furthermore, the decision by experts was sometimes qualitative, sometimes subjective and not repeatable since the composition of the group of experts can be changed or some concerns had changed.

Conclusion

The proposed triage algorithm in this preliminary study can be used to assist the experts in the triaging decision since it is a scientific, systematic and repeatable method. In applying the 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 model.

The key attributes and their weights applied in the triage algorithm should be periodically adjusted to fit the situation of public health 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 use such as antiinflammatory and antirheumatic products etc. Consideration of modifying the triage algorithm to serve these types of drugs, such as adding more sublevels will support the effectiveness of the triage algorithm.

Another observation is that there are some differences among experts in their awareness of special drugs or ADRs. Some experts concern about new drugs where as others concern about drugs use in public health programs, since they come from different experiences and backgrounds.

The signal triage algorithm will increased its performance if the SDRs as the input of the algorithm are of high quality. Starting with the incomplete data from ADR reports in the ADR database can be useless, as one said, "Garbage in, garbage out". The signal detection algorithm also affects the signal triage. Applying other measures of disproportionality (e.g. proportional reporting ratio (PRR), Bayesian Confidence Propagation Neuron Network (BCPNN) instead of ROR can be reconsidered to increase the effectiveness of the signal triage method and signal detection process.

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