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Proactive Identification of False Alert for Drug-Drug Interaction

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***Abstract*—**Researchers of drug-drug interaction alert systems have often suggested that there were high overridden rate for alerts and also too false alerts. However, research about decreasing false alerts is scant. Therefore, the aim of this article attempts to proactive identification of false alert for drug-drug interaction and provide solution to decrease false alerts. This research involved retrospective analysis prescribing database and calculated false alert rate by using MYSQL and JAVA. Results of this study showed 17% of false alerts and the false alert rate in the hospitals (37%) was more than in the clinics. To conclude, this study described the importance that drug-drug interaction alert system should not only detect drug name but also detect frequency or route, as well as in providing solution to decrease false alerts.

***Keywords*—**drug-drug interaction, proactive identification, false alert

I. Introduction

THE drug-drug interactions (DDI) occur when the patient take two drugs which affect with each other. It may be due to affect drug absorption, drug metabolism or pharmacology and result in drug toxicity or treatment failure. For example, combining warfarin (an anticoagulant drug) and NSAID (Non-Steroidal Anti-Inflammatory Drugs) would increase the risk of hemorrhagic peptic ulcer [1]. So the drug-drug interactions are 20% to 30% of preventable adverse drug events [2]. And drug-drug interactions also induce to hospitalization of about 1-2.8% of total patients [3-5].

With the rapid development of the computerized physician order entry (CPOE) in recent years, it has been considered the most effective method to prevent medication errors [6]. And then DDI alert system which is one kind of clinical decision support systems was designed to help prescribe more safely. For instance, when the prescription contains drug-drug interaction, it provides an alert which contains detail drug-drug interactions information to the prescribers.

DDI alert system seems eliminate drug-drug interactions when the prescriber order the drugs. But in fact, from the prescribers' view for DDI alert system, there were 61% that they considered DDI alerts to increase prescribing safely, 44% they were satisfied with the accuracy and only 29% the DDIs alert was exactly what they need [7]. The satisfaction and usefulness is low so it maybe induce high override rate. Several studies (Payne,2002; Weingart 2003) had noted that there was high overridden rate (85%-90%) for the DDI alerts [8, 9].

There are several reasons for overriding DDI alerts like the prescribers considered irrelevant to the DDI alert in question, monitoring to prevent consequences of DDI, the bias of the route or frequency and so on. In short, there are too many alerts and also too false alerts. So it means the prescribers have been desensitized or doubted DDI alert system.

The cost of false alerts such as time wasting, low confidence for DDI alert system and the most serious is that it will affect patient safety indirectly, for instance, hospitalization or extending time for hospitalization. The cause of false alert is that current DDI alert system often only considers drug names. When the pharmacists or doctors confirm DDI, they also concern date, frequency, route and so on at the same time. So DDI alert system would determine more false alert than the pharmacists or doctors. The ideal DDI alert system should also check frequency, route, laboratory, vital signs and so on. About overriding and false alert, most studies suggested to turn off alerts [10]. However, little research has been polished about decreasing false alerts. The purpose of this study was to proactive identifying false alert for DDI and provides solution to decrease false alert.

II. Material And Methods

Select DDI rules

The research design was a retrospective analysis prescribing database. But, there were too many DDI rules which were designed by hospital. For example, basing on surveillance guideline for the management of DDI, there were 329 potential DDIs classified as potentially significant [11]. It was difficult to study all kinds of DDI rules at one time so we asked experts (doctors and pharmacists). They suggested to select DDI which are the combination of antibiotics and antacids because it could explain how important to detect frequency or route when DDI occurred.

According to Drug Interaction facts, the antibiotics are (Tetracyclines or Quinolones) and the antacids are (aluminum salt or magnesium salt). The subgroups of tetracyclines are tetracycline, doxycycline, minocycyline and so on. The

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subgroup of quinolones are ciprofloxacin, levofloxacin, norfloxacin and so on. When co-administration of antibiotics and antacids, it would decrease pharmacologic effects of antibiotics by decreasing gastrointestinal absorption of antibiotics. For example, the combination of tetracycline and antacids would decrease 90% bioavailability of tetracycline so DDI would induce to treat failure. The onset is rapid and severity is moderate. It is generally recommended to avoid the simultaneous use, or interval of 3-4 hours use [11].

Subject

Subject is National Health Insurance Research database in Taiwan (NHIRD).Taiwan started a single-payer National Health Insurance program on March 1, 1995. And there were about 22.60 million of Taiwan's 22.96 million population were enrolled on 2007. NHIRD contains registration files and original claim data for reimbursement such as details of ambulatory care orders or details of inpatient orders and provided to scientists in Taiwan for research purposes [12].

Our research used details of ambulatory care orders on 2002. During obtaining medication from NHIRD in Taiwan, we followed Health Insurance Portability and Accountability Act (HIPAA) and also didn't know the data which came from what hospital is. The patient and the hospital is de-identification.

Data collection

In Taiwan, one prescription would have several kinds of drugs. Figure 1 show that data were collected by using MySql. There were accounting total 238,928,817 prescriptions of the outpatients and one prescription took 3.8 drugs in average. Than we use JAVA to detect the combination of antibiotics and antacids on the same prescription. Finally, there were 1,715,579 DDI. It showed that if the hospital design the DDI alerts system, there would be 1,715,579 alerts to the prescribers

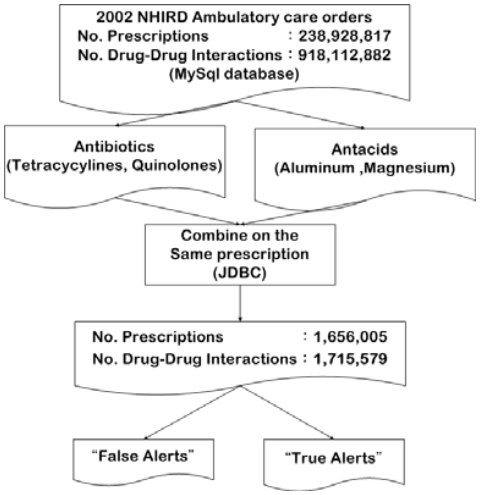

Fig. 1 Flowchart

As mentioned before, some alerts were false alerts. In view of pharmacists, they classified alerts as true alerts or false alerts. As show in the Table 1, there are three DDI alerts by only detecting drug name. But, the route of tetracycline is topical in example 2. It would not affect gastrointestinal absorption by topical tetracycline so it wouldn't induce DDI, the alert is false alert.

Similarly, example 3, the frequency of tetracycline is QDAM(taking in the morning) and aluminum salt is HS(taking before going to sleep). It means the patient would take the drugs at separate time so it would also not induce DDI. If DDI system shows a alert, it would be a false alert.

TABLE I
EXAMPLE FOR TRUE ALERT OR FALSE ALERT

Ex.	Drug Name	Form	Route	Frequency	Alert
1	Tetracycline	500mg Tablet	Oral	BID	"True Alert"
	Aluminumsalt	500mg Tablet	Oral	BID	
2	Tetracycline	3mg Ointment	Topical	BID	"False Alert"
	Aluminum salt	500mg Tablet	Oral	BID	
3	Tetracycline	500mg Tablet	Oral	QDAM	"False Alert"
	Aluminum salt	500mg Tablet	Oral	HS	

Assumptions

It was difficult for the pharmacists to check every prescription and then confirm true or false alert. So we define rules (following assumptions) for false alerts or true alerts. Next, we apply the rules to detect NHIRD and calculated false alerts.

"False Alert" :

Rule 1# Drug route :Topical
Rule 2# Drug Frequency: Separate administration every time
If the route of antibiotics or antacids were topical, it would be considered false alert (Rule 1). If the patient would took antibiotics and antacids at separating time, for example, figure 2 show that the frequency of antibiotics is TID (three times a day) and Antacids is HS (taking before going to sleep). It would be not taking the drugs at the same time so it would be also false alert. The definition of false alert is Rule 1 or Rule 2.

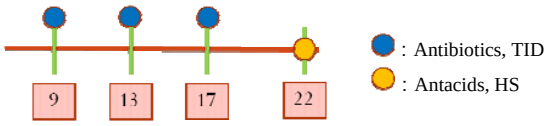

Fig. 2 Separate adminstration

"True Alert" :

Rule 3# Drug Route: Oral
Rule 4# Drug Frequency: Combine at least one time a day
True alert is that the route of antibiotics and antacids are oral and combining at least one time a day.

"Other" (Unable to determine)
Rule 5# Drug Frequency: ASORDER or PRN

ASORDER：When physicians prescribe such frequency, they will give additional direction about the time of administration.

PRN：Use when needed.

Because it couldn't confirm the time of administration from the database, it would be classified "Other".

III. Result

Based on the rules, there were 1,715,579 DDI alerts. As show in fig. 3, approximately 17.0% (292,115) of the alerts were "false alerts" and 81.2% (1,393,076) were "true alerts". Further analysis, fig. 4 presents that there were 11.2% "false alerts "for the clinics and 37.5% for the hospitals.

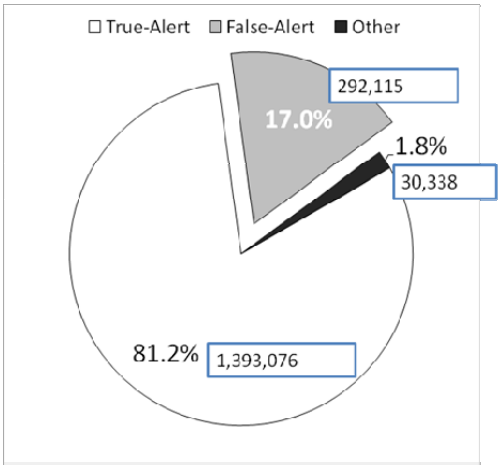

Fig. 3 DDI alerts

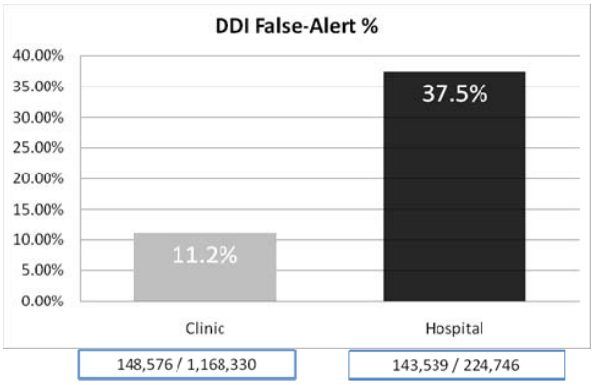

Fig. 4 Clinic and Hospital

IV. Discussion And Conclusion

In conclusion, there were 17.0% of false alerts and the false alert rate in the hospitals (37.5%) was more than the clinics (11.2%). The high false alert rate in hospital may be due to the prescribers in hospital would be told DDI. So they understood to prescribe the drug at separate time to avoid DDI.

Bases on clinical knowledge, DDI alert system should not only detect drug name but also drug frequency or route. But what is the meaning of detecting drug frequency or route in DDI alert system? So we could use detail drug-drug interactions to describe it.

First, the meaning of detecting route is that DDI alert system needs exclude topical and infused drugs. Because there would not be induce DDI, so DDI alert system should not alert it. Second, about detecting frequency, there were total 300 frequency combinations for combination of antibiotics and antacid on NHIRD. We could classify the combinations of frequency as overlapping or non-overlapping. After excluding topical and infused drugs, the DDI alerts system only needs to detect overlapping frequency.

For example, 124 overlapping frequency combinations such as Antibiotics BID (twice a day) and antacids BID had the overlapping time. So it means that it would only be DDI on overlapping frequency and it should be alert. The other non-overlapping frequency combinations is 176 such as antibiotics QDAM(taking in the morning) and antacids is HS(taking before going to sleep). About non-overlapping frequency, the patient would take the drugs at separating time. So it would not induce DDI.

Limitation

There were some limitations of this paper. First, it is the retrospective research so the prescribers may change prescription when he saw DDI alert in his hospital. However, there were over 90% overridden rate and the doctor took about 3 to 5 minute to see the patient in Taiwan. Second, it only focused on antibiotics and antacids so the prescribers may be in order to avoid the other potential DDI so modified the prescription. But it was difficult to determine the interaction from different DDI. Finally, it was similar to current research that this study research was hard to determine the adverse drug reaction.

Finally, this study research didn't focus on designing model to improve the overridden rate. It was proactive identification false alert and show how many false alerts for DDI alert system. Future research could be on different type DDI rules and then could offer the detail false alert to the pharmacists and medical management. They could base on detail information of the false alerts to choose the best way to add DDI rules or correct DDI model in their hospital.

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