Development and trial of the drug interaction database system

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Abstract

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Songklanakarin J. Sci. Technol., 2003, 25(4) : 525-534

The drug interaction database system was originally developed at Songklanagarind Hospital. Data sets of drugs available in Songklanagarind Hospital comprising standard drug names, trade names, group names, and drug interactions were set up using Microsoft® Access 2000. The computer used was a Pentium III processor running at 450 MHz with 128 MB SDRAM operated by Microsoft® Windows 98. A robust structured query language algorithm was chosen for detecting interactions. The functioning of this database system, including speed and accuracy of detection, was tested at Songklanagarind Hospital and Naratiwat-rachanagarind Hospital using hypothetical prescriptions. Its use in determining the incidence of drug inter-actions was also evaluated using a retrospective prescription data file. This study has shown that the database system correctly detected drug interactions from prescriptions. Speed of detection was approximately 1 to 2 seconds depending on the size of prescription. The database system was of benefit in determining of incidence rate of drug interaction in a hospital.

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บทคัดย่อ

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การพัฒนาและทดสอบระบบฐานข้อมูลอันตรกิริยาของยา
ว. สงขลานครินทร์ วทท. 2546 25(4) : 525-534

ระบบฐานข้อมูลอันตรกิริยาของยาได้เริ่มต้นพัฒนาขึ้นที่โรงพยาบาลสงขลานครินทร์ ชุดข้อมูลเกี่ยวกับยาที่มี
ใช้อยู่ในโรงพยาบาลสงขลานครินทร์ ได้แก่ ชื่อมาตรฐาน ชื่อการค้า ชื่อกลุ่ม และอันตรกิริยาของยาถูกสร้างขึ้นโดย
ใช้โปรแกรม Microsoft® Access 2000 เครื่องคอมพิวเตอร์ที่ใช้เป็นรุ่น Pentium III ความเร็ว 450 MHz และหน่วย
ความจำ SDRAM เท่ากับ 128 MB บนระบบปฏิบัติการ Microsoft® Windows 98 ขั้นตอนวิธีของการตรวจหา
อันตรกิริยาของยาใช้ภาษา SQL การทำงาน ความเร็วและความถูกต้องของการตรวจหาโดยระบบฐานข้อมูลถูกทดสอบ
ที่โรงพยาบาลสงขลานครินทร์และโรงพยาบาลนราธิวาสราชนครินทร์โดยใช้ใบสั่งสมมติ ระบบฐานข้อมูลได้ถูกทดลอง
ใช้เพื่อหาอุบัติการของอันตรกิริยาของยาโดยใช้ข้อมูลใบสั่งยาย้อนหลัง การศึกษานี้ได้แสดงให้เห็นว่าระบบฐานข้อมูล
สามารถตรวจหาอันตรกิริยาของยาจากใบสั่งยาได้อย่างถูกต้อง ความเร็วของการตรวจหาอยู่ระหว่าง 1 ถึง 2 วินาที
ขึ้นกับขนาดของใบสั่งยา ระบบฐานข้อมูลสามารถนำไปใช้ประโยชน์ในการหาอัตราอุบัติการของอันตรกิริยาของยาใน
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Drug-drug interaction is one cause of adverse reactions leading to an increase in risk of hospitalization and in health care costs (Hamilton *et al.*, 1998; Shad *et al.*, 2001). With a continuing increase in the list of drugs capable of interactions, detection of an interaction from prescriptions by hand, especially in a hospital, is impractical and liable to error. Computers have, therefore, been used to assist in process of detection for many years and have been proved to enhance the ability of practitioners to detect drug interactions (Morrell *et al.*, 1977; Tatro *et al.*, 1979; Greenlaw, 1981; Kinney, 1986; Haumschild *et al.*, 1987)

In western countries, many drug interaction screening computer systems have been widely developed, either as the database system for implementation into the hospital online monitoring system (Tatro *et al.*, 1975; Hulse, 1976; Greenlaw & Zellers, 1978; Shin *et al.*, 1983; Moore *et al.*, 1984; Haumschild *et al.*, 1987; Grönroos *et al.*, 1997), or as a stand-alone computer program (Jankel & Martin, 1992; Poirier & Giudici, 1995). Developing countries seem to have a limited capacity to develop the database. Only one study about the development of a drug interaction database has been documented and it is a stand-alone type (Bajaj *et al.*, 1994).

In Thailand, computer programs normally used in a hospital are mainly for management of drug stocks in the Pharmacy Department. Without a drug interaction computer program, or a proper database, an interaction can be detected only by hand, and investigation of incidence of drug interactions in prescriptions in hospitals is limited. In addition, the development of surveillance program for drug interaction in hospitals is not feasible.

Purchasing a drug interaction database from abroad for use in Thai hospitals is very expensive. More importantly, the imported one may be incompatible with the system in use in the hospitals and the database may not cover all drugs available locally. In our opinion, a drug interaction database for Thai hospitals should be set up. It should be intentionally developed for public. Knowledge can be shared or exchanged and the algorithm should be compatible with most hospital prescrib-

ing systems.

Recently, one of our colleagues has reported a search algorithm for a real-time detection of drug interaction and drug allergy (Wongpoowarak, 2002). It was designed via structured query language (SQL), nowadays a widely used database management language. This algorithm is very simple and robust, and can be used as a stand-alone system or incorporated into the present hospital prescribing system. Simulation study for speed performance indicated that this algorithm is well behaved.

The aims of this study were to describe the drug interaction database system developed at our university and to test whether the system using SQL-algorithm could detect drug interactions in real-time. It was also aimed to evaluate use of the database system to determine the incidence of drug interaction for pharmaco-epidemiological purposes.

Methods

Computer system

A drug interaction database system was developed using Microsoft® Access 2000 (Thai edition) on a Pentium III computer running at 450 MHz with 128 MB SDRAM operated by Microsoft® Windows 98.

Knowledge base

The knowledge base was developed on the basis of the concept described in previous study (Wongpoowarak, 2002). The system consists of a knowledge base and an algorithm. The knowledge base comprised four essential data sets, namely a standard drug name data set, a trade name data set, a group name data set, and a drug-drug interaction data set. A list of all drug names available in Songklanagarind Hospital, an academic hospital situated in Prince of Songkla University, was retrieved from the computer system of the Pharmacy Department of the hospital. Those hospital drug names were originally described as trade name, generic name, or local name followed by strength and dosage form (e.g. Inderal 40 mg tab). They were changed to equivalent standard drug names and collected in the data set (e.g. Inderal 40 mg tab → Inderal).
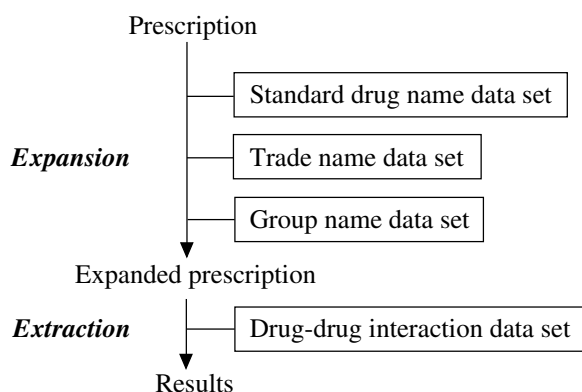
Each standard drug name presented as trade name in the standard drug name data set was transformed to an equivalent generic name based on the prescribing information handbook MIMS (Hor, 1995; 1999) and Songklanagarind Hospital Formulary (Tangkietgumjai & Prukpitikul, 1995) and placed in the trade name data set (e.g. Inderal → Propranolol). Generic names were classified according to pharmacological groups (e.g. Propranolol → Beta blockers) based on a textbook (Hardman *et al*., 1996). Group names were given corresponding to those used by the drug interaction information sources. The generic names and their groups were put into the group name data set.

The drug-drug interaction data set was developed based on three well-known information sources, viz., Drug Interaction Facts (Tatro, 2000), Evaluation of Drug Interactions (Zucchero *et al*., 1999), and Hansten and Horn's Managing Clinically Important Drug Interactions (Hansten & Horn, 1998). The list of potential interacting drug pairs, significance of interaction (i.e. rating of significance, onset of effects, severity of the interaction, and documentation that the interaction occurs clinically), pharmacological effect, mechanism, and management of interaction, and title of reference and page cited were included in this data set. Drug Interaction Facts was used as a main source. Any drug interaction list that appeared in the other two sources mentioned, but did not appear in Drug Interaction Facts were then added into the knowledge base.

Algorithm of detection

The detection of drug-drug interactions was performed using a two-stage SQL algorithm. Concept and process are described in detail elsewhere (Wongpoowarak, 2002). In brief, (Figure 1), a list of prescribed drugs in a prescription was expanded to equivalent names based on the data sets of standard drug names, trade names, and group names. Interactions were extracted by using the drug-drug interaction data set.
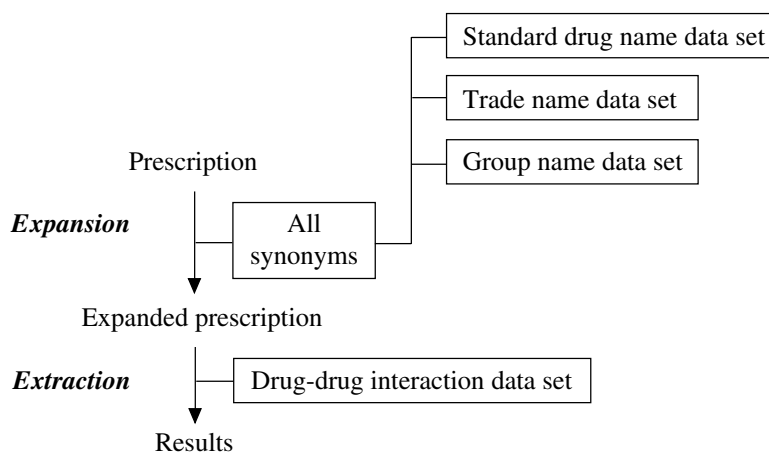
Songklanagarind Hospital

Prescription

Standard drug name data set

Expansion   Trade name data set

Group name data set

Expanded prescription

Extraction   Drug-drug interaction data set

Results

Naratiwatrachanagarind Hospital

Standard drug name data set

Trade name data set

Group name data set

Prescription

Expansion   All synonyms

Expanded prescription

Extraction   Drug-drug interaction data set

Results

Figure 1. Stages of algorithm of drug-drug interaction detection

Testing of the database system

The database system was tested at Songklanagarind Hospital by running on a stand-alone personal computer. The data were manually input into the computer. Speed of detection was tested using hypothetical prescriptions containing 2, 4, 8, 15, and 30 drug items. Accuracy of the database was also tested by using 15 4-drug-containing hypothetical prescriptions. Accuracy of detection was re-checked with the related information sources. The system was also tested with a retrospective 1-month outpatient prescription data file retrieved from the hospital computer system for determining the incidence of potential drug interactions.

The system was also tested at Naratiwatrachanagarind Hospital, a general hospital located in Naratiwat Province. Likewise, it was run on a stand-alone personal computer to test the speed of detection by using a hypothetical prescription containing 30 drug items and a retrospective 1-year outpatient prescription data file retrieved from the hospital computer system.

Results

A standard drug name data set was developed by including all 1,477 drug items in Songkla-

nagarind Hospital by the time the study was carried out. With trade name transformation, there were 1,260 records of trade name-generic name in the trade name data set. After classification of generic names, there were 960 records of generic name-group name in the group name data set. By collecting information of drug interaction from three information sources, there were altogether 1,714 records of interactions in the drug interaction data set. The information of pharmacological effect, mechanism, and management of each drug interaction was translated into Thai.

Prescriptions with various sizes, viz., 2, 4, 8, 15, and 30 drug items per prescription, were tested for detection speed. The result showed that the prescriptions were checked for any possible interactions. Output was reported in approximately 1 second for prescription size of 2, 4, 8, and 15, and almost 2 seconds for those of 30. A sample of a simply-designed graphic output is shown in Figure 2. Output was displayed as monographs one

by one. Each one contained a pair of interacting drugs and details of interaction according to the information source cited.

The detection of any potential interactions from 15 hypothetical prescriptions by using the database system showed correct results regarding the information presented in the information sources. Among the interactions, a few of them were found as self-interactions which were interactions between different drugs combined in the same preparation (i.e. Isoniazid [Rifinah®] vs. Rifampin [Rifinah®]) and between the same drug classified into more than one group (i.e. NSAIDs [Aspent®] vs. Salicylates [Aspent®]).

The detection of a 1-month data set of outpatient prescriptions containing totally 28,464 prescriptions was run on a stand-alone personal computer using the Windows operating system. The system was able to report interacting drug pairs and significance of the interactions in each prescription of the patient as shown in Table 1.

Prescription number	Drug1[a]	Drug2[b]	
1	Methotrexate (MTX 2.5 MG TAB)	Probenecid (PROBENECID 500 MG)	
Significance level[c]	**Onset[d]**	**Severity[e]**	**Documentation[f]**
1	Rapid	Major	Probable

Effect

ระดับยา Methotrexate ในพลาสมา ฤทธิ์ในการรักษา และความเป็นพิษของยาอาจเพิ่มขึ้น

Mechanism

Probenecid ลดการขับถ่ายยา Methotrexate ทางไต

Management

อาจจำเป็นต้องลดขนาดยา Methotrexate และเพิ่มระยะเวลาการใช้ยา Leucovorin เพื่อหลีกเลี่ยงการเกิดพิษจากยาเมื่อมีการใช้ยา Probenecid ร่วมด้วย เฝ้าสังเกตระดับยา Methotrexate ในซีรัมและปรับขนาดยาให้เหมาะสม

Reference	Page
Drug Interaction Facts	801

[a,b] **Interacting drug pair expressed as a group or generic name. Prescribing drugs (hospital drug names) are shown in parentheses.**
[c,d,e,f] **Significance of interaction defined according to the information source. Here, significance rating 1 represents a severe and well-documented interaction.**

Figure 2. Output of detection of interaction between Methotrexate and Probenecid by the drug interaction database system

Table 1. Sample of drug interaction detection report of one-month prescription data produced by the database system

HN[a]	Rxid[b]	Rxdate[c]	Dept[d]	Drug1[e]	Drug2[f]	Rx1[g]	Rx2[h]	Significance[i]
0000052	00072	01/10/2000	Med	Beta Blockers	Felodipine	METOPROLOL 100MG (BETALOC)	PLENDIL 10MG (FELODIPINE)	5
0000091	00127	01/10/2000	Med	Sulfonylureas	Salicylates	GLIPIZIDE 5 MG (MINIDIAB)	ASA 60MG	2
0000828	00917	02/10/2000	Med	Loop Diuretics	NSAIDs	FUROSEMIDE 40 MG TAB (LASIX)	ASA 60MG	3
0000939	01049	02/10/2000	Med	ACE Inhibitors	Salicylates	RENITEC 20 MG (ENALAPRIL)	ASA 60MG	4
0006866	07029	08/10/2000	Ped	Methotrexate	Sulfonamides	MTX 2.5MG TAB	COTRIMOXAZOLE TAB	1

[a] Encrypted hospital number of patients
[b] Prescription number
[c] Prescription date
[d] Department in which the prescription was issued
[e, f] Interacting drug pair expressed as a group or generic name
[g, h] Interacting drug pair expressed as a hospital drug name
[i] Level of significance of interaction regarding to the information source

Other related information, such as pharmacological effect, mechanism, and management of the interactions were not shown here.

A trial of using the database system to detect drug interactions in 1-month prescription data showed the possibility of determining the incidence of potential drug interactions in a hospital. Primary data shows that the incidence (number of prescriptions with drug interaction/number of prescriptions with two or more drugs * 100) was 8.70% overall and 0.30% for those which were potentially the most significant (significance level 1).

At Naratiwatrachanagarind Hospital, the system was also run on a stand-alone personal computer separately from the routine hospital prescribing system to avoid interference to the normal work. The algorithm of detection was also based on SQL but operated on a DOS system. Details of the detection process were slightly modified from that of Songklanagarind Hospital as follows (Figure 1). The data sets of standard drug names, trade names, and group names were combined into one synonym data set. The synonyms in the data set that were associated to the prescribing drugs were looked for. Drug interactions were detected using the drug interaction data set using the same method as that used at Songklanagarind Hospital. Real-time detection of any interactions in a hypothetical prescription containing 30 drug items was completed within 2 seconds. For the detection of a one-year prescription data set retrieved from the hospital computer system and containing some 300,000 drug items in some 108,000 prescriptions, the whole detection process took about 30 minutes.

Discussion

The drug interaction database system originated from Songklanagarind Hospital was developed during this study period. Knowledge base of trade names and generic names covered all drugs available locally. Most of them are also commonly used in other Thai hospitals. Drug interaction knowledge base included an extensive list of interacting drug pairs documented in selected foreign sources. In this study, interactions between

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any drugs and non-drugs such as food, alcohol, smoking, diseases, herbals, laboratory tests, and a patient (drug allergy) have not yet been included. Drug interaction information was translated into Thai to be helpful for Thai users. Title of information source and page cited were included and displayed in the detection output. This allows users to search for the original information if they need. The SQL algorithm used in this database system is the public domain algorithm in SQL to detect drug interactions and drug allergy with robustness and conforms to all ideal criteria for a good algorithm. These are 1) knowledge independence from software, 2) interconnectability between different knowledge bases, 3) knowledge expandability in real time usage or easily updated, 4) flexibility to all kinds of interactions, and 5) computation resource efficiency (Wongpoowarak, 2002).

This study has shown that the drug interaction database system was able to detect the interactions accurately. Connection of information among knowledge bases is very important. Either wrong or missed connection leads to failure of detection. This is the case with synonyms, for example, 'aluminium salts' (Europe) or 'aluminum salts' (USA). Additionally, generic names or group names, which are transcribed from hospital drug names, have to correspond with interacting drug names expressed in the drug interaction knowledge base. This poses a great challenge to database maintenance when the knowledge base is updated. Even a slight difference in spelling would lead to failure. This can be overcome to a large extent by spelling-tolerant software; however, we have not yet included that in the package.

Correctness of content in the database mainly depends on the information sources. In this study, the information sources used for the drug interaction knowledge base were secondary sources, from which information was collected and summarized by a group of qualified health-care professionals. We selected the information sources with which Thai hospital pharmacies are familiar. Among those sources, Drug Interaction Facts seems to be the most cited among Thai hospitals. Three sources were included in the study in order

to compile as much information as possible. During the development we noticed disagreement among information sources used. Not all drug interaction pairs were listed in every information source and there was a difference among the sources in listing their significance rating. Our finding is in good agreement with that of Fulda *et al*. (2000) that there are discrepancies in the listing and clinical significance rating for drug-drug interactions among the leading drug information sources. The authors suggested the need to develop methods for resolving discrepancies based on review of scientific evidence.

The database system rapidly detected drug interactions from prescriptions containing up to 30 drug items within 1 to 2 seconds depending on prescription size. According to our preliminary data, the average number of drug items per prescription was 2.5 at Songklanagarind Hospital, and 3.0 at Naratiwatrachanagarind Hospital. At these sizes of prescription, or slightly larger, the database system required about 1 second for detection process. Although the speed test was performed outside the normal prescribing system, that time scale implies, in real situation, screening and warning of potential drug interactions could occur immediately after a new drug is entered and would not interfere with the normal prescribing system.

The prescription size of 30 used in the speed test is unlikely under normal prescribing conditions. However, it is not unusual that a patient receives more than one prescription during each hospital visit, or has been taking a certain prescribing drug(s) prior to receiving another different one(s) during a certain period of time. In these situations, interaction across prescription (among different prescriptions of single patient) could occur. The size of prescription will be larger than normal if detection across prescription is involved. The speed test showed that detection from such a large prescription still required very short period of time.

There was a slight difference in algorithm between drug interaction database systems used in the two hospitals. At Songklanagarind Hospital, data sets of standard drug names, trade names, and group names were independent, while at Nara-

tiwatrachanagarind Hospital they were included in the synonym data set before starting the detection. Both algorithms showed acceptable results in the speed test. Users can adopt either of them. However, independence of the knowledge base of the algorithm used at Songklanagarind Hospital will allow knowledge base editing or updating to be done with ease, when this database system is in use in the hospital in the future.

In this study, the drug interaction database system reported all levels of significance of interaction as well as self-interaction. Practically, such reporting may be annoying when this system is used in hospitals since only the most potentially significant interactions should be signaled to avoid intrusion in the normal prescribing routine. Those problems need to be solved. Solution for over-reporting of all significant levels may be to set up a clinical study to screen only the most clinically significant interactions (this is included in our next study). Self-interaction can be solved by adding a single step of checking and suppressing such minor interactions before reporting the final result.

The drug interaction database system of this study contained an algorithm that can be used as a stand-alone system or implemented into the source code of the present drug distribution system (Wongpoowarak, 2002). It differs from another Thai-version drug interaction computer program, which has recently been marketed, as the latter is a stand-alone system and has not been designed for implementation into the hospitals. The database system is also different from MIMS Interactive software that has a specific section on drug-drug interaction which is an English version and suitable for use as stand-alone only. Additionally, to detect drug interactions from a hospital prescription with those computer programs, prescribing drugs must be entered as a trade name or generic name, even though they are normally prescribed as hospital drug names.

The database system of this study, therefore, would be advantageous for detection of drug interactions in hospitals. Detection output (for example, as shown in Figure 2) can alert pharmacists or physicians to take precautions to avoid drug interactions. An appropriate intervention (such as using a low dose, changing to a safer drug, or carefully monitoring a patient) can be done promptly. Risk of adverse consequences due to drug interactions to the patients would be reduced. Evaluation of its efficiency in controlling drug interactions should be done after real implementation.

In addition to the capability of the database system in detecting drug interactions in prescriptions, this study has shown that it can be used in determining of incidence of drug interactions in a hospital. Data on incidence of drug interaction in Thailand are limited. This database system can resolve the problem of the lack of an efficient tool for detection in the past, causing limitations in reporting the incidence of drug interactions in hospitals in Thailand.

The drug interaction database system developed originally at Songklanagarind Hospital can be utilized by the public. The system is suitable for Thai hospitals or users because its knowledge base includes a list of drugs available in most Thai hospitals, and information of drug interaction is expressed in Thai. Other hospitals can use the database system by developing their own standard drug name knowledge base. Trade name and group name knowledge bases developed at Songklanagarind Hospital can also be used with some addition of deviating drug information at any particular hospital. The drug interaction knowledge base can be used directly. The algorithm can be implemented in any prescribing system that is compatible with SQL language. Independence of data sets allows the updating of knowledge bases, which is essential for a reliable system, and then implementation becomes easy. This study shows that the modularization of database components is feasible, but the reporting system has to be resolved for real implementation.

Conclusion

This study showed the ability of the database system developed initially at Songklanagarind Hospital in real-time detection of drug interactions

from prescriptions. It is likely the database system is applicable to other Thai hospitals. The study also showed its potential for being a tool in pharmaco-epidemiological study of drug interactions in Thailand. Real implementation of this database system into the routine prescribing system of the hospital may be needed to further justify its benefit to the health system. The authors plan to use this database system as a tool to investigate drug interactions in Songklanagarind Hospital in the next study.

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