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ORIGINAL ARTICLE

Potential drug interactions in dermatologic outpatient prescriptions—experience from nationwide population-based study in Taiwan

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ABSTRACT

Background: Adverse drug reactions increase morbidity and mortality, and potential drug interactions (DIs) increase the probability of adverse drug reactions.
Objectives: To survey the potential DIs of dermatologic outpatient prescriptions from the National Health Insurance Research Database of Taiwan.
Methods: All prescriptions written by dermatologists in 2000 were analyzed to identify potential DIs among drugs appearing on the same prescription sheet.
Results: Of 150.6 million prescription sheets with 669.5 million prescriptions registered in the National Health Insurance Research Database of Taiwan, we identified 6.6 million (4.4%) dermatology prescription sheets with 19 million (2.8%) prescriptions. The findings of the study showed that 283,458 potential DIs were found in this category, accounting for 1.49% per prescription. The most common significance Level 1 interaction (1.1%) was between the less-sedative antihistamines (terfenadine/astemizole) and azole antifungal agents. Among the category of severity, the most common was terfenadine interacting with cimetidine and ketoconazole (4.4%), followed by astemizole interacting with cimetidine and ketoconazole (2.9%). The most common drug class interaction occurred between corticosteroids and antacids (48.5%). Overall, DI incidence in dermatologic patients was lower than that of the general patient population.
Conclusions: Based on the study findings, we concluded that dermatologists need to be reminded of having possible potential DIs when prescribing medications. Introducing information technology into the computerized physician order entry system into the daily practice may reduce potential DIs.

Introduction

Drug interactions (DIs) may cause treatment failure or side effects, and subsequent adverse drug reactions (ADRs) may cause considerable mortality and morbidity. From a meta-analysis of prospective studies in the United States, fatal ADRs are ranked as the fourth to sixth leading causes of death in hospitalized patients.[1] Furthermore, deaths due to medical errors are found to exceed the number attributable to the eighth leading cause of death in the United States.[2] In a study from the National Health Service in the United Kingdom, 400 patients died or were seriously injured in adverse events involving medical devices. The National Health Service study also indicates nearly 10,000 people were reported to have experienced serious ADR.[3] An estimated 5–6.5% of inpatients have ADR[1,4] and 2.5–4.4% of them originally have DIs.[5]

The mean length of hospital stay and costs of hospitalization are increased significantly in patients with ADRs compared with those without.[6] During hospitalization, drug complications are the most common ADR type, accounting for 19% of cases.[7] Although 70.5% of patients with ADR become disabled for less than 6 months, 2.6% developed permanent disabilities and 13.6% led to death.[8]

An estimated 1.46–35% outpatients may develop ADRs and 13% of them may have serious drug reactions.[9,10] The finding of a DI study on a sample database from the National Health Insurance

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(NHI) database of Taiwan showed the potential DI prevalence was 30%. Among the potential DI pairs, 42,193 (9.9%) pairs were classified as Level 1 clinical significance, representing 3% of all prescriptions. The five most common potential DI pairs in the clinically significant Level 1 category are digoxin/furosemide, digoxin/trichlormethiazide, isoniazid/rifampin, digoxin/amiodarone, and warfarin/aspirin.[1]

Not every health care provider can distinguish potential DIs from ADRs and take corrective measures accordingly. In a survey study, Glassman et al[11] found that only 44% (ranging from 11% to 64%) clinicians have correctly identified all drug-drug pairs. The clinician's understanding of DI can help decrease ADR, safeguard patient safety, and avoid associated medicolegal problems.

Medications often cause cutaneous reactions,[12] although the severe forms of drug eruption are rare and account for less than 5% observed in hospitalized patients.[13] Andersen and Feingold[14] reviewed the mechanism of adverse DIs' action of risky drugs such as methotrexate, cyclosporine A, antifungal agents, antibiotics, retinoids, and antihistamines. As many new drugs enter or exit the market, Barranco[15–17] has updated a biennial list of clinically significant DIs in dermatology and offered strategies to identify potential DIs. However, the epidemiologic investigation for the DI prevalence rate is still lacking. In a study of potential DIs in outpatient prescriptions based on a large-scale database, the French team reported that two dermatologic prescription pairs with potential DIs (cisapride/imidazole antifungals and retinoids/tetracyclines) can increase risks of ventricular arrhythmia and intracranial hypertension, respectively.[5] Learning DI profiles is necessary to avoid subsequent ADRs when prescribing medications.

In this study, we surveyed the quantities and related information of prescriptions with potential DIs in dermatologic outpatient prescriptions for 1-year period.

Methods

We analyzed dermatologic prescriptions in Taiwan from January 1 to December 31, 2000 to identify potential DIs among drugs on the same prescription sheet.

Implemented in 1995, the NHI program is a compulsory NHI system that covers almost the whole population of Taiwan.[18] The NHI claims of computerized information for all outpatient prescriptions written by all physicians (general practitioners, specialists, dentists, and traditional Chinese physicians) are kept in the National Health Insurance Research Database and are released to researchers for epidemiological studies.[19,20]

The Bureau of National Health Insurance maintains a large-scale database of all organizations, physicians, insured clients, procedures, medications, prescriptions, and costs of both inpatient and outpatient treatments. A monthly updated NHI drug formulary forms the basis of reimbursement for hospitals and clinics, and more than 21,000 pharmaceutical references have been validated by the Bureau of Pharmaceutical Affairs of the Department of Health. Because of the redundancy of the pharmaceutical references, the lists of drug have been reclassified by the same formulation regardless the type of preparations. The revised drug formulary has 1600 pharmaceutical formulations. A DI database was developed in which potential DIs were defined according to the drug pairs in the *Drug Interaction Facts, 2001 ed*.[21] The significance rating was made up by the summary of onset, severity, and documentation of each DI. By this definition, the level of significance for a DI is rated from a scale of 1–5. A rating of 1 is major in severity with the effects of potentially life-threatening and with certain documented evidences, whereas a rating of 5 is unlikely evidenced or only limited data in resulting minor severity.[22] Of 9328 DI pairs, 1048 pairs are classified as significance Level 1 and 3347 pairs Level 2 (Table 1).

Health care facilities in Taiwan are classified into four types—medical centers, regional hospitals, local hospitals, and private practice clinics. They are defined by the scales, number of beds, and quality of medical and nursing care. The categorizing task is managed by the Taiwan Joint Commission of Hospital Accreditation, a quasi-official body supported by the Department of Health of Executive Yuan of Taiwan. The rate of reimbursements differs because of the different type of organizations that could provide financial support to the hospitals.

We analyzed and identified the prescription drugs with potential DIs among drugs that appeared on the same prescription sheet by cross-checking with the revised drug list and potential DI database using Structured Query Language procedures under MySQL v4.018 database server platform (Sun Microsystems, Santa Clara, CA, USA). We excluded interactions that involved two or more different dosages or frequencies of the same drug.

The NHI prescriptions written by all dermatologists from January 1 to December 31, 2000 were analyzed. The identifiable patient data were censored to insure patient confidentiality. The following relevant data were extracted from each prescription sheet including patient ID, date of birth, clinic ID, facility type, prescribing physician ID, number of drugs, generic pharmaceutical ingredients regardless of the formulations (i.e. systemic or topical), diagnosis (in International Classification of Disease, Ninth Revision, Clinical Modification codes), and dispensing pharmacist ID. From those data, we also generated the following attributes such as DI pair, significance rating, severity level, documentation level, and DI effects.

We performed descriptive statistical analysis using SAS 8.02 (Institute Inc., Cary, NC, USA).

Results

In 2000, we identified 150,560,023 prescription sheets with 669,449,835 prescriptions administered to the Bureau of National Health Insurance. We identified 6,651,820 (4.4%) dermatologic prescription sheets with 19,047,309 (2.8%) prescriptions in 4,947,346 patients. The mean number of drugs per sheet was 2.84 ± 0.04.

We found 283,458 prescriptions with potential DIs, representing 1.49% per prescription and 4.26% per sheet. Most DIs are clinically irrelevant and negligible with significant interactions only

Table 1 Significance rating scale of potential drug interactions.[21,23]

Significance	Severity[a]	Documentation[b]
1	Major	Established, probable, or suspected
2	Moderate	Established, probable, or suspected
3	Minor	Established, probable, or suspected
4	Major/moderate	Possible
5	Minor	Possible
	Any	Unlikely

[a] Severity: Major: life-threatening or permanent damage; Moderate: deterioration of patient's status; Minor: bothersome or little effect.

[b] Documented literature: Established: proven to occur in well-controlled studies; Probable: very likely, but not proven clinically; Suspected: may occur, some good data, needs more study; Possible: could occur, but data are very limited; Unlikely: doubtful, no good evidence of an altered clinical effect.

[1] Lin MS, Chang NC, Yang KYH, Chen YH. The potential drug-drug interactions in an ambulatory prescription data in Taiwan. *The 20th International Conference on Pharmacoepidemiology and Therapeutic Risk Management*. Bordeaux, France, 2004: 36.

accounting for 1.44%. The most frequent DIs and percentage of significance levels are summarized in Tables 2 and 3, respectively.

Among significance Level 1 DIs, the interactions between less-sedative antihistamines (terfenadine and astemizole) and azole antifungal agents were the most common (1.1%). As shown in Table 4, this combination increased potential risk of cardiotoxicity. As for interactions of major severity, terfenadine's interactions with cimetidine and ketoconazole were ranked first (4.4%), followed by astemizole's interactions with cimetidine and ketoconazole (2.9%). Those interactions would also result in potential risk of increased cardiotoxicity (Table 5). The most commonly involved pairs of drug type in DIs were interactions of corticosteroids and antacids (48.5%) with significance Level 5 (Table 6).[24]

Among the relationship of DIs and organization types, we found more DIs occurred in private practice with prevalence of 1.60%. DI incidence in this study was higher in the regional hospital group, followed by the local hospital group (Figure 1). The prevalence of DIs decreased after 40 age of years peaking at the fourth decade (1.63%).

Discussion

The patient safety issues were brought to attention in a report "*To Err is Human*", published by the Institute of Medicine.[2] The problems of ADRs, especially DIs, have also been reviewed in general medicine but not much in dermatological field in recent years. Dermatologists are increasingly faced with complex problems of drug eruptions due to the high prevalence of polypharmacy in their daily practice. Unlike ADRs that are often unpredictable, DIs can be avoided if physicians take extra precautions in prescribing. The data in this study are thought to be the first large-scale investigation of potential DIs of dermatologic outpatient prescriptions in a nationwide population involving 4.9 million patients and 19 million prescriptions. The result of this study showed that 4.26% of these prescriptions will develop potential DIs, an estimate of one DI in every 17 patients. This incidence rate of DI occurring in dermatologic outpatient prescriptions was lower compared with the general population.

The interactions of gastrointestinal medications (antacids and histamine-2 antagonists) account for nearly two-third of total DIs. The most common DI involved interactions with aluminum hydroxide and account for over half of the all interactions (54.2%), and followed by the interactions of cimetidine. With regards to drug class, the top interaction pair was antacid and corticosteroids (48.5%), systemically or topically administered. This could reflect the high prevalence of prescribing such combination in Taiwan, although the significance level is 5 and the interaction results in mild decrease in the pharmacologic effect of corticosteroids.[21] Interestingly, there were 8724 (3.1%) interactions of aluminum hydroxide and cimetidine, which are always used for peptic ulcer medications, that rank 11th in DI pairs (not shown) that cimetidine might be considered as an antihistamine.

The concurrent administration of antibiotics and metal ions, such as calcium, aluminum, zinc, or bismuth, may result in clinically significant impairment of gastrointestinal absorption and therefore reduce the anti-infective response.[14,15,21,25] Tetracyclines and quinolones are examples of the oral antibiotics that interact with metal ion contained in antacids. In this study, the combined use of aluminum antacid and doxycycline/minocycline occurred in 22,199 (7.8%) prescriptions that might develop potential DI. Optimally separating the ingestion times between the antibiotics and metal ion may reduce the extent of interaction.

Drugs that affect hepatic metabolism might interact with antibiotics. The interactions occur because of modification of hepatic metabolism related to either enzyme inhibition or enzyme induction. Enzyme inhibition occurs when metabolism of one drug is inhibited by another drug that is being administered concurrently. In contrast, enzyme induction occurs when the metabolism of one drug is increased by another drug that is being administered. The enzymes most commonly affected are components of the cytochrome P450 (CYP 450) metabolic enzyme system, and CYP3A4 is

Table 3 Drug interaction profiles.

Significance	Onset[a]	Severity	Documentation	*n*	%
1	Rapid	Major	Established	13	1.44
			Probable	50	
	Delayed	Major	Established	419	
			Probable	3209	
			Possible	399	
2	Rapid	Moderate	Established	120	29.85
			Probable	894	
			Suspected	293	
	Delayed	Moderate	Established	205	
			Probable	47,615	
			Suspected	35,474	
3	Rapid	Minor	Probable	1056	1.14
			Suspected	609	
	Delayed	Minor	Probable	1500	
			Suspected	63	
4	Rapid	Major	Possible	66	6.47
		Moderate	Possible	72	
	Delayed	Major	Possible	17,656	
		Moderate	Possible	555	
5	Rapid	Moderate	Unlikely	7	61.10
		Minor	Possible	5806	
			Unlikely	14	
	Delayed	Moderate	Unlikely	12,781	
		Minor	Possible	153,498	
			Unlikely	1084	
Total				283,458	100

[a] Onset of drug interactions: Rapid: within 24 hours; Delayed: days to weeks.

Table 2 Top 10 drug interactions for the general population.

Drug A	Drug B	Significance	*n*	%	Overall %[a]
Betamethasone	Aluminum hydroxide	5	67,858	23.94	0.30
Dexamethasone	Aluminum hydroxide	5	43,729	15.43	0.19
Triamcinolone	Aluminum hydroxide	5	11,362	4.01	0.05
Minocycline	Aluminum hydroxide	2	11,299	3.99	0.05
Doxycycline	Aluminum hydroxide	2	10,900	3.85	0.05
Terfenadine	Cimetidine	4	10,578	3.73	0.05
Doxycycline	Cimetidine	5	10,129	3.57	0.04
Ketoconazole	Cimetidine	2	8929	3.15	0.04
Minocycline	Phosphate	2	8873	3.13	0.04
Cimetidine	Aluminum hydroxide	5	8724	3.08	0.04

[a] Total potential drug interactions: 22,812,747.

Table 4 Significance Level 1 drug interactions.

Drug A	Drug B	*n*	%
Terfenadine	Ketoconazole	1879	0.66
Astemizole	Ketoconazole	1188	0.42
Oxacillin	Tetracycline	175	0.06
Dexamethasone	Rifampin	174	0.06
Betamethasone	Rifampin	132	0.05
Ampicillin	Doxycycline	83	0.03
Terfenadine	Erythromycin	75	0.03
Oxacillin	Doxycycline	73	0.03
Gentamicin	Furosemide	48	0.02
Triamcinolone	Rifampin	42	0.01

Table 5 Top five drug interactions of major severity.

Drug A	Drug B	Significance	*n*	%
Terfenadine	Cimetidine	4	10,578	3.7
Astemizole	Cimetidine	4	6998	2.5
Terfenadine	Ketoconazole	5	1879	0.7
Astemizole	Ketoconazole	5	1188	0.4
Oxacillin	Tetracycline	1	175	0.1

the most common subfamily enzyme system involved in both inhibition and induction of drug metabolism.[14,15,25] Macrolides and rifamycin antibiotics frequently develop such interactions.[15] Interactions between corticosteroids and rifampin, a rifamycin antibiotic, occurred in 348 prescriptions that account only 0.12% of DIs in dermatology, which may have resulted in decreased pharmacologic and toxic effect of corticosteroid.[21]

Few potentially life-threatening risks were encountered among all DIs from this study. The results showed that interactions of second-generation antihistamines such as terfenadine and astemizole were ranked first (7.3%), which can potentially cause QT prolongation in electrocardiography and/or cardiotoxic risk. Fortunately, those drugs are seldom used now and there are more safe nonsedative antihistamines available. Although patients with skin problems are generally considered to have a minor illness, the results of this study showed that in 1 year more than 3000 dermatologic patients in Taiwan were exposed to the risk of arrhythmia through their dermatologic medications. The findings of our study show that interactions of azole antifungal agents (ketoconazole/itraconazole) and other drugs had 1.09% of all dermatologic DIs. Sixteen drugs have been frequently referred as "red flag" drugs in drug metabolism and DIs[17]. They have been found to account for 56 of the 70 clinically significant DIs (80%) in Barranco's[17] most recent study. Of 16 drugs, just 3 red flag drug families (azole antifungal agents, macrolide antibiotics, and serotonin reuptake inhibitors) have accounted for 41 of the total 70 DIs (58%).[17] The result of our study shows similar finding and lends support to Barranco's study.[15,17] In our study, 46 (0.02%) interactions with methotrexate were found, including nonsteroidal anti-inflammatory drugs and sulfonamides that might induce increased methotrexate toxicity or bone marrow suppression, respectively,[21] but no interactions of azathioprine, cyclosporine, and retinoids that always being concerned were found. Based on our findings, we suggest that dermatologic patients may expect higher safety standards to cope with their diseases.

Evidence shows that computerized DI screening systems reduce DIs and adverse drug events (ADEs).[11,26,27] It has been suggested that the electronic medical record and computerized physician order entry systems that alert the clinicians contributed to the decreased incidence of potential DIs and related ADEs.[28] These computerized medication alert systems are implemented more widely in medical centers than in other type of health care facilities. It is further speculated that such safety mechanism is the reason

Table 6 Top 10 drug interactions by drug class.

Drug Class A	Drug Class B	Significance	*n*	%
Corticosteroids	Antacids	5	137,596	48.54
Tetracyclines	Cimetidine	5	12,776	4.51
H-2 antagonists	Antacids	5	10,289	3.63
Indomethacin	Antacids	5	4042	1.43
Mefenamic acid	Magnesium salts	5	2561	0.90
Benzodiazepines	Antacids	5	2395	0.84
Acetaminophen	Anticholinergics	5	1610	0.57
Cimetidine	Anticholinergics	5	665	0.23
Phenothiazines	Aluminum salts	5	650	0.23

H-2 = histamine-2.

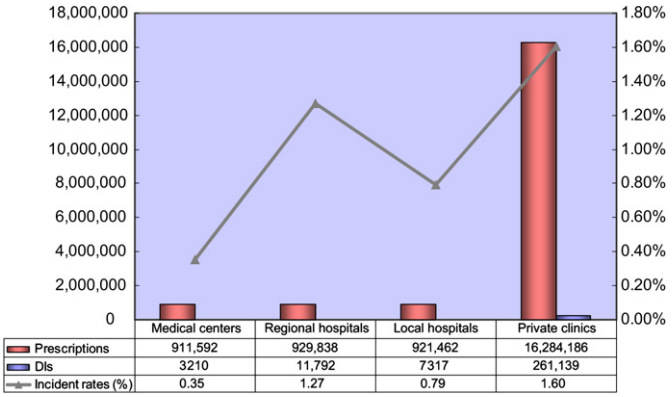

Figure 1 Relationship of prescriptions, drug interactions, and facility type.

why medical centers have lower DI incidence than that of other health care facilities.

With the developments in genetic engineering and biotechnology within the past 10 years, there are multiple bioengineered agents being used to treat immune-mediated disorders such as rheumatoid arthritis, psoriasis and psoriatic arthritis, ankylosing spondylitis, and pemphigus. The application of such biologic agents is increasing, and the potential interaction with other therapeutic modalities is another important issue that clinicians will wrestle with not only because of long-term use of such agents but also the patients may lie about their immunocompromised status. Although the interactions of these agents were not found in our study, as the agents were not widely used at the time of data collection and few evidences showed the potential interactions between different biologic agents, awareness should be taken when prescribing these medications.[29]

Study limitations

The findings of our study should be interpreted with caution because of the limitations below: first, our study focused only on potential DIs in outpatient prescriptions, and we did not attempt to survey the real occurrence of DIs and corresponding ADEs resulting from DIs. Second, we did not evaluate some important factors that would contribute to ADEs with DIs. Those factors include patient age, genetics, comorbidities, major organ function status, and drug compliance.[30] Third, we assessed only prescriptions on a single sheet, but not interactions with other medications prescribed on the other sheets of the same patient or the same periods of time. Furthermore, all generic pharmaceutical ingredients were taken as one regardless of its formulations, so the potential DIs might be over- or underestimated. Because of those weaknesses, we suggest that the incidence of potential DIs may be underestimated in our study population. Researchers who plan to do a future study on this topic should consider addressing these study limitations.

Conclusion

By having analyzed a large-scale database, we can understand the incidences, significance levels, severity levels, and drug types of potential DIs in dermatologic outpatient prescriptions. Although the DI incidence rates are low, we would like to remind dermatologists of the potential DIs when prescribing medications. To reduce potential DIs, we suggest introducing or integrating information technology into the computerized physician order entry system into the daily practice.

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