Application of a Data-Mining Technique to Analyze Coprescription Patterns for Antacids in Taiwan

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ABSTRACT

Background: Although antacids are popular drugs with a long history of use, their true utilization patterns—including over-the-counter use—have rarely been documented. Because all antacids are reimbursed under the National Health Insurance program in Taiwan, it is possible to access and analyze nationwide data for these drugs.

Objectives: The purposes of this study were to estimate the scale of antacid prescribing in Taiwan using the national insurance claims for outpatient services and to analyze coprescribing patterns of antacids using modern data-mining techniques.

Methods: The National Health Insurance Research Database in Taiwan supplied the visit-based sampling data sets, which had a sampling ratio of 0.2% for all claims for outpatient medical services in the year 2000. In addition to the plain statistics (ie, data from simple calculations) for antacid prescriptions, we also analyzed relationships between prescriptions for antacids and nonantacid drugs. A data-mining technique—association rule mining—was applied to identify the drugs prescribed in combination with antacids.

Results: Among a total of 409,049 eligible prescriptions for 1,704,595 drug items to be administered orally, antacids were present in 213,494 prescriptions (52.2%). Antacid users were generally older than nonusers (mean [SD] age, 39.9 [23.4] years vs 32.4 [25.7] years). In all, 88.8% of antacid items (189,531/213,494) were prescribed without claims diagnoses of gastrointestinal

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disorders. Using association rule mining with a 1.0% minimum support factor, there were 36 strong association rules between prescriptions for antacids and other drug subgroups at the third level of Anatomical Therapeutic Chemical classification. Nonsteroidal anti-inflammatory drugs and drugs for treating upper respiratory infections played dominant roles in the associations with antacid prescriptions; vitamin B complex and antivertigo preparations were also strongly associated with antacids.

Conclusions: Antacid coprescriptions were common in Taiwan in the year 2000. Further study should investigate whether antacid prescribing patterns are influenced by Taiwanese perceptions that Western drugs injure the stomach. (*Clin Ther.* 2003;25:2453–2463)

Key words: antacids, association rule, data mining, coprescription, insurance claims database, pharmacoepidemiology.

INTRODUCTION

Antacids are popular drugs with a long history of use.[1] However, because they are nonprescription (over-the-counter) drugs, their true utilization patterns have rarely been documented.[2–6] Among the developed countries, only the Scandinavian countries, the Czech Republic, and Slovakia have supplied information about nationwide consumption of antacids in recent years.[7] In Taiwan, the National Health Insurance (NHI) program, which covers nearly the entire population (21,400,826 beneficiaries at the end of 2000), was started in 1995.[8] Because the liberal policy of the NHI program allows reimbursement for antacids, it is now possible to access and analyze data about antacid prescribing patterns.

In the current study, we performed a survey of NHI claims for outpatient services in Taiwan to estimate the scale of antacid prescribing in the general population. Because antacids are not only used as ulcer-healing agents but are also taken to alleviate the dyspepsia caused by other drugs (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]), we included in our study an analysis of the coprescribing patterns of antacids (ie, the classes of drugs with which antacids were most frequently coprescribed). To find an answer to this question in a database with millions of records, we needed to apply advanced computing techniques to our analysis. Data-mining techniques, especially association rules,[9–13] were used in our calculations.

MATERIALS AND METHODS

In 1999, the NHI began to release claims data to the public for the purpose of academic research. The NHI Research Database (NHIRD) project is managed by the National Health Research Institutes in Taiwan (an organization similar to the

National Institutes of Health in the United States). Through this project, dozens of extracted data sets have been made available for each year beginning with 1996. Any identification data (ie, patient names and institutions) in the data sets available to researchers have been encrypted to protect privacy. The encryption is consistent across all data sets, so original identification numbers are unique, making longitudinal follow-up feasible. The data sets are similar to those provided by the Medical Expenditure Panel Survey and National Ambulatory Medical Care Survey in the United States. Researchers who wish to access NHIRD data sets must sign a user agreement form indicating they will obey related regulations and acknowledge the NHIRD in their publications. According to Taiwan's personal-data privacy legislation and the regulations of the institutional review board (IRB) at Taipei Veterans General Hospital (Taipei, Taiwan), use of such encrypted data sets is exempt from the IRB approval procedure.

In the current study, we analyzed 2 sampling files from the year 2000 (S_CD20000 and S_OO20000), which represented the linked visit and prescription files, respectively. A prescription may contain several drug items (generally, 4 drug items per prescription in Taiwan). These 2 files were extracted from the complete database of outpatient claims (excluding services for dental and traditional Chinese medicine) using a sampling ratio of 0.2%. The sampling was random and visit based but was separated by month to avoid seasonal deviations that could arise from random sampling. After a visit had been sampled, prescription items belonging to that visit were then extracted. According to the NHIRD, these sampling files were representative of all utilization within the NHI in Taiwan. The structure and contents of NHI claims files have been described.[14,15]

We obtained a complete file of approved drugs in Taiwan from the NHI. Different brands, strengths, and forms of each drug were officially assigned a unique code for use in the claims file. The Bureau of NHI has published a list of Anatomical Therapeutic Chemical (ATC) codes[16] for each drug.

The sampling visit file contained 526,693 records and the sampling prescription file 2,574,739 records. Our study included only regular visits and refill prescriptions; items such as emergencies, outpatient operations, dialysis, tuberculosis treatment, home care, and preventive services were excluded. Furthermore, our analysis focused only on drugs taken orally. In our study, antacids were defined as drugs with the ATC subgroup code A02A. These antacids comprised 8 fourth-level subgroups: magnesium compounds (A02AA); aluminum compounds (A02AB); calcium compounds (A02AC); combinations and complexes of aluminum, calcium, and magnesium compounds (A02AD); antacids with antiflatulents (A02AF); antacids with antispasmodics (A02AG); antacids with sodium bicarbonate (A02AH); and other combinations of antacids (A02AX).

To identify the disorders for which antacids were indicated, we used claims diagnoses with *International Classification of Diseases, Ninth Revision, Clinical Modifi-*

cation[17] codes 530 (diseases of the esophagus), 531 (gastric ulcer), 532 (duodenal ulcer), 533 (peptic ulcer, site unspecified), 534 (gastrojejunal ulcer), 535 (gastritis and duodenitis), 536 (disorders of stomach function), 537 (other disorders of stomach and duodenum), 578 (gastrointestinal hemorrhage), 787.1 (heartburn), and 789.0 (abdominal pain).

The database software IBM DB2 Universal Database for Windows NT version 7.1 (IBM Corporation, White Plains, New York) was used for data linkage and initial processing. The data-mining software IBM DB2 Intelligent Miner for Data Version 6.1 (especially the associations mining function[18,19]) was used to analyze the antacid coprescriptions.

Association rule mining, also known as *market basket analysis,* was originally developed in the 1990s to identify which groups or sets of items were likely to be purchased together.[20,21] Applied to prescriptions, an association rule would be as follows: When a physician prescribes drug A (or drugs $\{A_1, A_2\}$, drugs $\{A_1, A_2, A_3\}$, and so forth), then he will also prescribe drug B in X% of cases and this coprescribing is present in Y% of all prescriptions.[18] The *support factor* is the ratio of coprescriptions to all prescriptions (ie, Y% in the above example). The *confidence factor* is the ratio of coprescriptions to prescriptions for drug A (ie, X% in the above example).

Data mining is an iterative, exploratory process. In executing the program to identify association rules in our data set, we initially chose 0.1% as the minimum support factor and 1.0% as the minimum confidence level. Antacids were the item constraints (ie, only association rules containing antacids would be included). To attain the threshold support for efficient computing, we categorized individual drugs according to the ATC classification. We calculated the association rules of antacids with other drug items that were categorized at the third level of the ATC codes. Ordinarily, to obtain a reasonable number of association rules, the computation is repeated several times with different thresholds of support and confidence. The association rules (or relationships) discovered with data-mining techniques might be either coincidental or causal. To clarify the relationship between antacids and coprescribed drugs, we finally narrowed the calculation by limiting the minimum confidence to the frequency of antacids in all prescriptions. The univariate comparison was tested using the Student *t* test for continuous variables (patients' age). $P < 0.05$ (2-tail test) was considered statistically significant.

RESULTS

Among 409,049 eligible prescriptions, 1,704,595 drug items were to be administered orally. Of these items, 232,999 were antacids (13.7%), listed in 213,494 prescriptions (52.2%). In this visit-based, cross-sectional data set, 51.4% of male patients (94,372/183,727) and 53.6% of female patients (114,867/214,482) took antacids (Table I). Antacid users were generally older than nonusers (mean [SD] age, 39.9 [23.4] years vs 32.4 [25.7] years; $P < 0.001$, Student *t* test).

Table I. National Health Insurance outpatient prescription claims (visit-based sampling ratio, 0.2%) for oral drugs in Taiwan in the year 2000.

Variable	All Prescriptions	Prescriptions With Antacids	Prescriptions Without Antacids
Prescriptions, no. (%)	409,049 (100.0)	213,494 (52.2)	195,555 (47.8)
Prescribed drug items, no. (%)	1,704,595 (100.0)	992,045 (58.2)	712,550 (41.8)
Prescribed antacid items, no. (%)	232,999 (100.0)	232,999 (100.0)	–
Patients,* no. (%)	400,303 (100.0)	210,487 (52.6)	189,816 (47.4)
Female	214,482 (53.6)	114,867 (54.6)	99,615 (52.5)
Male	183,727 (45.9)	94,372 (44.8)	89,355 (47.1)
Sex unknown	2094 (0.5)	1248 (0.6)	846 (0.4)
Mean (SD) age, y	36.3 (24.8)	39.9 (23.4)†	32.4 (25.7)

*Because this analysis used a visit-based sampling data set, frequent users of medical services might have been sampled more than once.

†$P < 0.001$ versus antacid nonusers, Student t test.

Our analysis identified 8995 different oral drugs belonging to 163 third-level ATC subgroups. The top 20 third-level subgroups are listed in Table II, grouped by prescribed item count and the number of prescriptions containing each drug subgroup. These 20 subgroups accounted for 78.0% of the total prescription items. Antacids ranked as the most frequently prescribed subgroup of drugs.

Only 35,544 prescriptions (8.7%) carried diagnoses of peptic ulcers or other gastroduodenal disorders for which antacids might be indicated. Antacids were found in 23,963 prescriptions of this kind, meaning that 88.8% (189,531/213,494) of antacid items were prescribed without related diagnoses of gastrointestinal disorders specified on the claims. Moreover, only 1408 prescriptions (0.3%) contained just antacids.

On the assumption that antacids might be prescribed to alleviate or prevent the potential adverse effects caused by other drugs, we used the data-mining software to search for situations in which antacids were coprescribed. Using the initial thresholds of support (0.1%) and confidence (1.0%), we obtained 980 association rules of drug-item sets (in ATC third-level codes) with which antacids were coprescribed. Among them, 83 rules were 1-to-1 associations, 373 were 2-to-1, 376 were 3-to-1, 147 were 4-to-1, and 1 was 5-to-1. When we further confined the rules to having ≥1.0% support and exceeding the expected confidence factor of antacids (52.2%), 36 strong association rules remained. In Table III, these rules are stratified by the number of item sets and listed in order of the confidence factor. One interesting finding was that among the 1-to-1 association rules, muscle relaxants (M03B) had a higher antacid coprescribing rate than NSAIDs (M01A) (77.5% vs 69.3%). Other drug groups with a high antacid co-

Table II. The most frequently prescribed drugs at the third level of the Anatomical Therapeutic Chemical (ATC) classification among 1,704,595 drug items (from 409,049 prescriptions) in Taiwan in the year 2000.[16]

Drug Subgroup	ATC Code	Drug Items, no. (%)	Prescription Occurrences, no. (%)
Antacids	A02A	232,999 (13.7)	213,494 (52.2)
Antihistamines for systemic use	R06A	161,250 (9.5)	129,477 (31.7)
Other analgesics and antipyretics	N02B	124,534 (7.3)	116,208 (28.4)
Anti-inflammatory and antirheumatic drugs, nonsteroidal	M01A	112,557 (6.6)	105,151 (25.7)
Expectorants, excluding combinations with cough suppressants	R05C	86,465 (5.1)	77,299 (18.9)
Cough suppressants, excluding combinations with expectorants	R05D	81,109 (4.8)	73,576 (18.0)
Cough suppressants and expectorants, combinations	R05F	67,787 (4.0)	60,987 (14.9)
Nasal decongestants for systemic use	R01B	62,900 (3.7)	59,787 (14.6)
Adrenergics for systemic use	R03C	61,340 (3.6)	57,404 (14.0)
β-lactam antibacterials, penicillin	J01C	51,677 (3.0)	51,253 (12.5)
Other β-lactam antibacterials	J01D	47,556 (2.8)	47,361 (11.6)
Anxiolytics	N05B	36,279 (2.1)	33,423 (8.2)
Other antiasthmatics for systemic use	R03D	31,218 (1.8)	29,929 (7.3)
Propulsives	A03F	29,189 (1.7)	28,370 (6.9)
Corticosteroids for systemic use, plain	H02A	27,180 (1.6)	26,881 (6.6)
Macrolides and lincosamides	J01F	24,487 (1.4)	24,359 (6.0)
Antithrombotic drugs	B01A	25,005 (1.5)	23,823 (5.8)
Drugs for treatment of peptic ulcer	A02B	22,752 (1.3)	21,844 (5.3)
Other cold combination preparations	R05X	22,707 (1.3)	21,588 (5.3)
Antiflatulents	A02D	21,221 (1.2)	21,171 (5.2)
Other		374,383 (22.0)	

prescribing rate included vitamin B complex (A11E, 64.2%), antivertigo preparations (N07C, 60.9%), and anxiolytics (N05B, 58.9%).

DISCUSSION

Although we used sampling data sets, the size of the database made our study larger than most other antacid studies.[2–6] Antacid prescribing was found to be popular in Taiwan. Of all prescriptions for oral drugs for outpatients, 52.2% (213,494/409,049) included antacids; however, diagnoses of gastroduodenal disorders were specified only in 8.7% of all prescriptions (35,544/409,049).

The prevalence of gastroduodenal disorders might be either underestimated or overestimated in our analysis. A maximum of 3 diagnostic codes were supplied

Table III. Associations of nonantacid drug item sets (in the third-level codes of the Anatomical Therapeutic Chemical [ATC] classification[16]) with antacid prescriptions in Taiwan in the year 2000.*

Confidence Factor, %	Support Factor, %	Drug Class (ATC Code)
1-to-1 association*		
77.5	3.8	Muscle relaxants, centrally acting drugs (M03B)
69.3	17.8	Anti-inflammatory and antirheumatic, nonsteroidal drugs (M01A)
64.2	1.6	Vitamin B complex, including combinations (A11E)
63.3	1.2	Belladonna and derivatives, plain (A03B)
60.9	1.7	Antivertigo drugs (N07C)
60.2	17.1	Other analgesics and antipyretics (N02B)
58.9	4.8	Anxiolytics (N05B)
57.6	3.8	Corticosteroids for systemic use, plain (H02A)
57.3	3.3	Antithrombotic drugs (B01A)
55.6	3.9	Propulsives (A03F)
54.9	1.0	Peripheral vasodilators (C04A)
54.5	6.8	β-lactam antibacterials, penicillin (J01C)
54.2	1.1	Antipropulsives (A07D)
53.9	6.2	Other β-lactam antibacterials (J01D)
53.4	3.2	Macrolides and lincosamides (J01F)
2-to-1 association*		
82.0	2.9	Anti-inflammatory and antirheumatic drugs, nonsteroidal drugs (M01A) + muscle relaxants, centrally acting drugs (M03B)
79.3	1.8	Anti-inflammatory and antirheumatic drugs, nonsteroidal drugs (M01A) + anxiolytics (N05B)
68.6	1.4	Anxiolytics (N05B) + other analgesics and antipyretics (N02B)
67.7	4.1	Anti-inflammatory and antirheumatic drugs, nonsteroidal drugs (M01A) + other analgesics and antipyretics (N02B)
64.6	2.2	Anti-inflammatory and antirheumatic drugs, nonsteroidal drugs (M01A) + β-lactam antibacterials, penicillin (J01C)
64.6	2.2	Anti-inflammatory and antirheumatic drugs, nonsteroidal drugs (M01A) + other β-lactam antibacterials (J01D)
61.5	2.1	Anti-inflammatory and antirheumatic drugs, nonsteroidal drugs (M01A) + cough suppressants and expectorants, combinations (R05F)
59.7	2.7	Other β-lactam antibacterials (J01D) + other analgesics and antipyretics (N02B)
59.2	2.0	Anti-inflammatory and antirheumatic drugs, nonsteroidal drugs (M01A) + nasal decongestants for systemic use (R01B)
59.0	1.2	Other analgesics and antipyretics (N02B) + macrolides and lincosamides (J01F)
58.7	3.1	Other analgesics and antipyretics (N02B) + β-lactam antibacterials, penicillin (J01C)
56.4	3.0	Other analgesics and antipyretics (N02B) + cough suppressants and expectorants, combinations (R05F)

(continued)

Table III. (Continued)

Confidence Factor, %	Support Factor, %	Drug Class (ATC Code)
55.8	1.1	Other analgesics and antipyretics (N02B) + other antiasthmatics for systemic use (R03D)
55.8	3.4	Antihistamines for systemic use (R06A) + anti-inflammatory and antirheumatic drugs, nonsteroidal drugs (M01A)
55.6	1.9	Anti-inflammatory and antirheumatic drugs, nonsteroidal drugs (M01A) + expectorants, excluding combinations with cough suppressants (R05C)
54.6	1.2	Cough suppressants and expectorants, combinations (R05F) + other antiasthmatic drugs for systemic use (R03D)
53.9	2.0	Anti-inflammatory and antirheumatic drugs, nonsteroidal drugs (M01A) + cough suppressants, excluding combinations with expectorants (R05D)
53.1	1.4	Cough suppressants and expectorants, combinations (R05F) + β-lactam antibacterials, penicillin (J01C)
53.0	2.6	Other analgesics and antipyretics (N02B) + nasal decongestants for systemic use (R01B)
52.8	1.9	Antihistamines for systemic use (R06A) + corticosteroids for systemic use, plain (H02A)
3-to-1 association*		
53.6	1.1	Antihistamines for systemic use (R06A) + other analgesics and antipyretics (N02B) + cough suppressants and expectorants, combinations (R05F)

Confidence factor = ratio of coprescriptions to prescriptions for a particular drug or a set of drugs; support factor = ratio of coprescriptions to all prescriptions.
*Association rules: Drug or ($Drug_1$ + $Drug_2$) or ($Drug_1$ + $Drug_2$ + $Drug_3$) or ... → antacids (A02A).

on each visit record for claims to the NHI; therefore, not all disorders were documented. The claims diagnoses were used only for the insurance reimbursement and were not verified, especially for the outpatient sector. They were sometimes only tentative diagnoses to justify the prescriptions. Similarly, the actual utilization of antacids in Taiwan might be either underestimated or overestimated in our analysis. Antacids have always been nonprescription drugs, and the level of their use in self-medication remains unknown. However, even if antacids were prescribed and dispensed, complete patient compliance could not be guaranteed.

Our approach using association rule mining to identify coprescriptions with antacids was a new attempt in the field of pharmacoepidemiology. Based on the assumption that antacid prescriptions were related to the use of other drugs rather than to gastrointestinal diseases, we did not use the claims diagnoses in our computations. Thus, the cause–effect relationships between diagnosis and antacid prescription were hidden. Furthermore, associations between drugs should

be judged separately based on medical knowledge. Even if an association rule is strongly significant, it is not always useful. This situation has been recognized in the field of data mining,[21] and NSAIDs provide a good medical example.[14] With their notorious upper gastrointestinal tract adverse effects[22] and their large volume of prescriptions, NSAIDs seemed to play a predominant role in the results of our association rule mining. However, the high antacid coprescription rates of muscle relaxants and anxiolytics might be explained by the frequency of their combination with NSAIDs, which could be observed in the 2-to-1 association rules. Some other rules were related to upper respiratory tract infections, which accounted for a large proportion of outpatient consultations. However, the strength of unsupervised data mining is the discovery of interesting information that could not be obtained from large databases through intuition or traditional methods of data analysis. Vitamin B complex and antivertigo preparations were among the interesting associations identified in our analysis. Patients receiving these drugs might be prone to gastric disorders, or the reverse could be true: vitamin B complex may have been used to prevent potential vitamin B_{12} deficiency associated with the chronic acid suppression of antacid use. The association rules found in data mining are not strict rules in the biomedical sense and must be verified in further studies.

In our experience, perceptions in Taiwan (and perhaps elsewhere in the Orient) foster the belief that Western drugs injure the stomach. Both qualitative and biochemical analyses are needed to determine whether the habit of prescribing antacids in Taiwan is based on such perceptions or whether it is conditioned by the acidity of other drugs.[23,24] Furthermore, various data-mining techniques have begun to be applied to the field of pharmacoepidemiology.[25–27] We hope our approach with a real-life example provides inspiration in this direction.

CONCLUSIONS

Our analysis found that antacid coprescriptions were common in Taiwan in the year 2000. Further research should investigate whether antacid prescribing patterns are influenced by Taiwanese perceptions that Western drugs injure the stomach.

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