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ORIGINAL REPORT

Usage of the claim database of national health insurance programme for analysis of cisapride-erythromycin co-medication in Taiwan†

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SUMMARY

Purpose: This study aimed to use the National Health Insurance Research Database, Taiwan for risk analysis of concomitant use of cisapride and erythromycin.

Methods: The sample consisted of subjects identified in the Outpatient Sampling Database (OSD) and Longitudinal Health Insurance Database 2000 (LHID 2000), derived from the original claim data of the National Health Insurance Research Database, Taiwan.

Results: According to the LHID 2000, a total of 464 individuals experienced 685 episodes of cisapride-erythromycin co-medication prescribed by 295 physicians, revealing a prevalence of 4.5% concomitant use, with higher prevalence in clinics (9.2%) than in other medical institutes (3.7–5.4%). Among the co-medication episodes, 81.9% and 61.2% were prescribed from the same health institutes and by the same physicians, respectively. No medical record of cardiac arrhythmias was found among these patients in 2001 and 2002, probably due to the fact that 78.9% of the 464 individuals were under age 16, 84.0% had short exposure duration (1–4 days) and 98.0% of the episodes were prescribed with a cisapride dose of less than 0.8 mg/kg/day.

Conclusions: Findings from this study suggest that there exists an urgent need for accreditation in terms of pharmacovigilance of clinical sites and their practicing physicians for the prevention of irrational concomitant prescription in Taiwan. Our findings also indicate that it is necessary to investigate other possible conditions of potentially dangerous co-medication in Taiwan and other developing countries. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — cisapride; erythromycin; co-medication; claim data; National Health Insurance Research Database

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INTRODUCTION

Cisapride has been used as an antiemetic for the treatment of gastrointestinal (GI) motility disorders.[1,2] It has been recommended by the American College of

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Gastroenterology Practice Parameters Committee Guidelines for the treatment of gastroesophageal reflux disease (GERD)[3] and had been prescribed to more than 140 million patients before 1999.[4] Although cisapride has never been indicated for the use in children under 12 years of age, it has been prescribed to over 36 million children worldwide between 1993 and 1999, of whom over 25 million were infants and newborn.[4] It has been recommended as the drug of first choice in children for treating GERD by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition.[4] However, a serious concern has been raised with the use of cisapride, and its association with serious cardiac arrhythmias, such as ventricular tachycardia, ventricular fibrillation, torsade de pointes, and QT prolongation.[5–7] Around 85% of the cardiac events reported, occurred in patients with known risk factors including concomitant use of other drugs causing QT prolongation, inhibiting cytochrome P450 3A4 (CYP3A4), or depleted serum electrolytes; or the presence of disorders that may have predisposed patients to arrhythmias.[6] Therefore, co-administration of the following medications should be avoided: (1) class Ia and class III anti-arrhythmic drugs, and some antipsychotics, which can elicit QT prolongation;[8–10] (2) CYP 3A4 inhibitors, such as macrolide antibiotics (e.g. erythromycin), azole anti-fungal agents, H_2 antagonists, certain antidepressants etc., which increase the plasma concentration of cisapride and consequently increase the cardiotoxicity. Cisapride's potential for serious cardiac arrhythmia led to the revision of indication and label warnings, and the subsequent voluntary withdrawal of the drug from the UK and the USA markets in 2000,[12,13] leaving cisapride to be only accessible by physicians following well defined protocols for specific treatment.[13]

Taiwan launched a single-payer National Health Insurance (NHI) programme on 1, March 1995. As of December 2003, 22.0 million individuals, 97% of Taiwanese population, were enrolled in this programme.[14,15] NHI's database system contains registration files, original claim data and reimbursement data. Large computerized databases derived from this system, maintained by fully trained scientists in the National Health Research Institutes (NHRI), Taiwan, are provided to scientists for research purposes. The database is a useful tool for the pharmacoepidemiology study of concomitant drug co-administration.

Although an alert on the cardiotoxicity and potential of drug–drug interactions of cisapride was announced by the Taiwan authority in 1999,[16] the rate of cisapride prescription remained high up to its withdrawal from Taiwan's market in 2004.[17] It is interesting to observe the prevalence of cisapride use and the risk of drug–drug interactions associated with cisapride, as well as observing the potential value of the databases derived from the claim database of NHI programme in Taiwan to analyse nation-wide prescribing patterns of cisapride. We chose to observe erythromycin prescription as the corresponding concomitant medication for this endeavour because of its widespread antibiotic use in Taiwan. In addition to its effect against gram-positive and some of the gram-negative bacteria, erythromycin has also been prescribed in the treatment of GERD.[18,19] The concomitant use of cisapride and erythromycin is contraindicated due to the serious adverse event of ventricular tachycardia reported as early as 1996.[20,21] In addition, the current study aimed to assess the sources of such prescribing incidences, and to determine to what extent such incidences were due to institutional or personal factors.

METHODS

Study population and data source

The National Health Insurance Research Database (NHIRD) consists of various sampling databases for cross-sectional as well as longitudinal studies, constructed from the registration files and original claim data collected by the NHI programme.[22] Registration files include registry for contracted health institutes, contracted specialty services, contracted beds, medical personnel, board-certified specialists, catastrophic illness patients, beneficiaries, as well as supplementary registry data. Basic demographic data of beneficiaries, as well as relevant data of health institutes, categorized by the Taiwan Joint Commission on Hospital Accreditation,[23] are also included in these files. Original claim data include monthly claim summaries for ambulatory care and inpatient service, ambulatory care expenditure by visits, details of ambulatory care orders, inpatient expenditures by admissions, details of inpatient orders, details of prescriptions, and expenditures for prescriptions dispensed at contracted pharmacies. In addition, medical diagnoses and clinical management are also included in these files.

All the data regarding any identification or personal information which may be used to identify patients and care providers such as medical institutions and physicians in the NHIRD were scrambled. This process was performed by the Bureau of National

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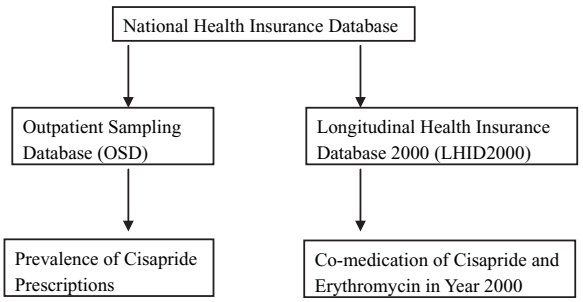

Figure 1. Flowchart of databases used for this study

Health Insurance (BNHI) before all claim data was transferred to NHRI. Therefore, it is impossible to query the data of individuals at any level according to the regulations in Taiwan. All the researchers using NHIRD and its' subset databases, are required to sign a written agreement to possess no intention of attempting to obtain information which could potentially violate the privacy of the patients and care providers.

We used two subsets of database, the OSD and LHID2000, retrieved from the NHIRD by the experts of NHRI (Figure 1). The details of database generation were described in the website of the NHIRD.[24] A brief description of these databases were provided as described below.

The Outpatient Sampling Database (OSD) consists of ambulatory care expenditures and the associated details of care orders by ambulatory visits. A systematic sampling method was applied to randomly sample a representative database of ambulatory care expenditures by visits from the entire database. The sampling rate is 0.2% and the size of the subset for each month is determined by the ratio of the amount of data in each month to that of the entire year. The OSD of each year is then obtained by combining the subsets for the 12 months of the year. We employed various methods to validate the representative of the OSD, which would demonstrate the validity of the OSD. For example, there was no significant difference in the distribution of patient visits in different specialties of clinics between the OSD and the original NHIRD (Chi square statistics $(\chi^2) = 44.62$, degree of freedom (df) $= 46$, $p = 0.530$).

The LHID2000 contains all the original claim data of 200 000 individuals randomly sampled from the Registry for Beneficiaries 2000 of the NHIRD, which maintains the registration data of any individual who was once a beneficiary of NHI programme during the period of 1996–2000. There are approximately 23 720 000 individuals in this registry. All the registration and claim data of these 200 000 individuals collected by the NHI programme constitute the LHID2000. The database has been used for related studies.[25] Again, we employed several methods to validate the representative of the LHID2000 before we conducted our analysis. For example, there was no significant difference in the gender ($\chi^2 = 1.74$, df $= 1$, $p = 0.187$) distribution between the patients in the LHID2000 and the original NHIRD.

Prevalence of cisapride prescriptions

The trend of cisapride prescriptions before and after the official alert on cisapride-related cardiac toxicities and drug interactions was analysed with data retrieved from the OSD. The number and distribution of cisapride prescriptions in different categories of health institutes during 1999–2002 were also evaluated. The number of cisapride prescriptions per 100 thousand beneficiaries was then extrapolated from the results obtained from the OSD.

Co-medication of cisapride and erythromycin in year 2000

The database used to evaluate cisapride-erythromycin interaction was the LHID2000. The prevalence of cisapride-erythromycin co-medication was analysed using mainly the claim data of ambulatory care during the period from 1, January 2000 to 31, December 2000 in the LHID2000. Detailed information about prescriber, date of prescription, unit content, dosage form, dose and frequency, duration of therapy, total quantity and health institutes were retrieved from the LHID2000. After cross-linkage with drug data files, the usage of cisapride and erythromycin in individual patients were determined. Approximately 3.0% of

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cisapride prescriptions and 5.1% of erythromycin prescriptions were excluded from this study due to lack of information in the duration of therapy.

It is known that cisapride has a mean elimination half-life of 6–12 h and is expected to be completely eliminated within 1–2 days.[26,27] Erythromycin has a much shorter half-life of 1–1.5 h and is completely eliminated within 1 day.[27] Therefore, cases of concomitant co-medication of cisapride and erythromycin is defined as the co-administration of both medications to the same patient on any single day.

Characteristics of physicians responsible for cisapride- erythromycin co-medication

As it is presumed that all physicians presumably alert to the cisapride-erythromycin interaction, a physician was considered to be responsible for the co-medication if he/she prescribed the prescriptions of both drugs to the same patient simultaneously or knowingly prescribed cisapride to a patient who had already received erythromycin prescribed by another doctor. We conducted a multivariate logistic regression analysis to determine if age, gender, medical specialty and practice site are predictors for cisapride-erythromycin co-medication. The health institutes were then divided into two groups: (1) clinic, and (2) medical centres, regional hospitals and local hospitals. Medical specialties were categorized into two groups: (1) internal medicine, pediatrics and family medicine; and (2) others.

Cisapride dosage analysis

The appropriateness of daily dosage per unit of body weight for cisapride usage was assessed. We estimated the daily dosage of cisapride for those whose data were missing by the quotient of total amount of cisapride prescribed over time length of prescription. For body weight, we estimated weight based on the gender and age distribution of patients. Fifty percentile of a growth nomogram of children and adolescent ($\leq$15 years), published by the Department of Pediatrics, National Taiwan University Hospital,[28] was used as a base for body weight estimation in patients under 16 years of age. For adults, the body weight used for dosage calculation was 50 kg for female and 70 kg for male.

Clinical outcomes of cisapride-erythromycin co-medications

The clinical consequences were assessed based on the diagnoses and subordinate diagnoses at medical visits made by patients in a 3-month period following the concomitant use of cisapride and erythromycin. Specifically, the diagnoses or subordinate diagnoses include any of ICD-9CM code 426 (conductive disorder), 427 (cardiac dysrhythmia), or 794.3 (nonspecific abnormal results of cardiovascular function study).

Statistical analysis

The software programme SAS, version 9.1 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. The pre-selected alpha value was at $P < 0.05$ level. The descriptive data was presented in frequency and percentage and 95%CI for proportions were calculated. The difference in binomial proportion among more than two groups was presented by chi-square statistics. The difference in binomial proportions between two groups was either presented by Z statistics or the Mantel-Haenszel odds ratios (OR) with 95%CI for OR.

RESULTS

Prevalence of cisapride prescribing

The number of cisapride prescriptions in the OSD database was 8191 in 1999 and declined to 5162 in 2000, 4428 in 2001, and 4216 in 2002. The number of cisapride prescriptions per 100 thousand populations in Taiwan was then estimated by extrapolation and is shown in Table 1. Most of the prescriptions (>50%) were prescribed by physicians in clinics. Using the data in 1999 as a control, a significant reduction of

Table 1. Estimated number of cisapride prescriptions per 100 thousand beneficiaries made by different categories of health institute in years 1999 to 2002. Data were retrieved from the OSD database

Health Institute*	Year			
	1999	2000	2001	2002
Medical centres	2217	1249	846	828
Regional hospitals	3176	1699	1309	1462
Local hospitals	3369	1427	1050	933
Clinics	9845	7260	6705	6161
Total	18 607	11 634	9910	9384

*The health institutes in Taiwan are categorized as medical centres, regional hospitals, and local hospitals, according to the accreditation programme held by Taiwan Joint Commission on Hospital Accreditation (TJCHA),[23] based on their number of beds, facilities, quantity and quality of medical personnel, quality of services, educational programme etc. However, clinics in Taiwan do not have any accreditation so far.

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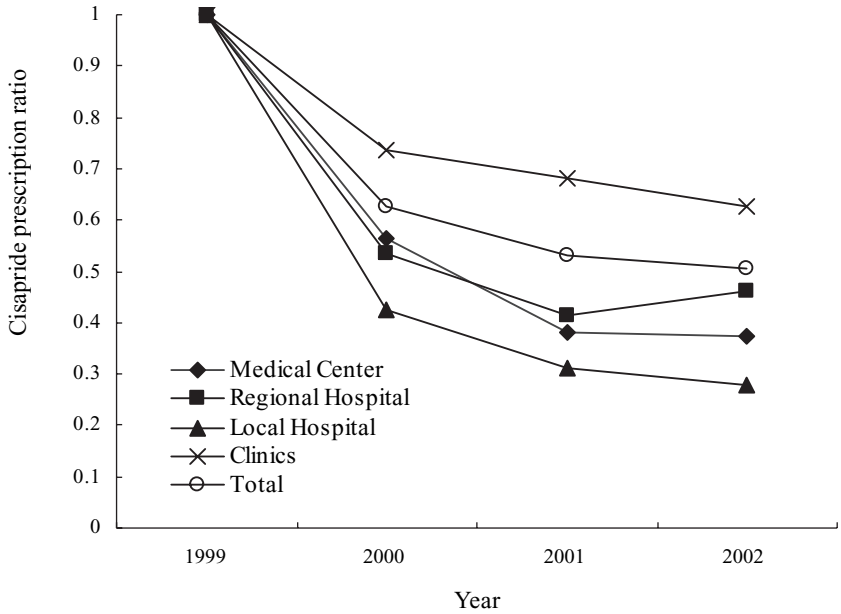

Figure 2. Ratio of cisapride prescription in 2000—2002 with respect to that of year 1999 for different categories of health institute, data from Table 1

cisapride prescription was observed from 1999 to 2000 (Figure 2). The reduction was highest in local hospitals (57.6%) and lowest in clinics (26.2%). The overall reduction from hospitals (49.9%) was significantly higher than from the clinics ($Z = 29.26$, $p < 0.001$). However, there still existed about 9384 cisapride prescriptions per 100 thousand beneficiaries in 2002 (Table 1), which constituted approximately 50% of the number of cisapride prescriptions in 1999.

Co-medication of cisapride and erythromycin in year 2000

According to the LHID2000 database containing 200 000 beneficiaries, we discovered that 10 258 individuals received 22 175 cisapride prescriptions in ambulatory settings, which constituted approximately 0.27% out of the total medication orders in ambulatory visits of the LHID2000. About 50.5% of cisapride users were children and adolescents younger than 12 years of age. There was a significant difference of gender distribution across the five age groups (Table 2). Males were more prevalent cisapride users aged 12 and younger, than those older than 12 ($\chi^2 = 100.89$, df = 1, $p < 0.0001$). Among the 10 258 individuals, 3285 individuals (32.0%) received a total of 9204 erythromycin prescriptions in the same year. The dates of cisapride prescription and erythromycin prescription for the same patient were compared in order to clarify the extent of cisapride and erythromycin co-medication exposure. A total of 464 individuals were identified to experience 685 episodes of concomitant drug use. As high as 78.0% of patients exposed to the potential risk of cisapride-erythromycin co-medication were at the age of 12 and younger (Table 2). Among the 464 individuals with co-medication, there was higher proportion of males in the age group of ≤ 12 than in the age group of >12 ($\chi^2 = 4.68$, df = 1, $p < 0.031$). Among cisapride users, there was no gender difference on the risk for co-medication in the ages 0–12 ($\chi^2 = 0.92$, df = 1, $p = 0.327$) or in the ages >12 ($\chi^2 = 0.00$, df = 1, $p = 0.951$). The nation-wide prevalence of cisapride-erythromycin co-medication was then estimated to be 4.5% in 2000.

The majority of cisapride prescriptions (63.3%) were made by medical physicians in clinics (Table 3), which was significantly higher than those from the other health institutes. Among the 685 cisapride-erythromycin co-medication episodes, 496 (76.9%) originated from clinics, while the remaining 139 episodes (23.1%) were from hospitals. The overall percentage of co-medication of cisapride-erythromycin among total cisapride prescriptions was 3.1%, which ranged from 2.1% in local hospitals to 3.5% in clinics (Table 3). As the values of 95%CI was compared, the prevalence of cisapride-erythromycin co-medication

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Table 2. Demographic data of total cisapride users and those who exposed to cisapride-erythromycin co-medications. Data retrieved from the LHID2000 database

	Cisapride users of different age group, patient number (%)					
	0∼12 years	13∼18 years	19∼45 years	46∼65 years	>65 years	All ages
All cisapride users[a]						
Total	5175 (50.5)	364 (3.6)	2103 (20.5)	1461 (14.2)	1155 (11.3)	10258 (100)
Female	2442 (47.2)	212 (58.2)	1304 (63.0)	813 (55.7)	556 (48.2)	5327 (51.9)
Male	2728 (52.8)	152 (41.8)	765 (37.0)	647 (44.3)	598 (51.8)	4890 (47.7)
Missing	5	0	34	1	1	41
Cisapride users who exposed to cisapride-erythromycin co-medications[b]						
Total	362 (78.0)	7 (1.5)	40 (8.6)	27 (5.8)	28 (6.0)	464 (100.0)
Female	162 (44.7)	5 (71.4)	24 (60.0)	15 (55.6)	14 (50.0)	220 (47.4)
Male	200 (55.3)	2 (28.6)	16 (40.0)	12 (44.4)	14 (50.0)	244 (52.6)
Incidence rate	7.00%	1.92%	1.90%	1.85%	2.42%	4.52%

[a]Gender difference across the 5 age groups ($\chi 2 = 168.15$, df = 4, $p < 0.0001$).
[b]No gender difference across the 5 age groups ($\chi 2 = 5.98$, df = 4, $p = 0.200$).

in clinics was found to be significantly higher than in other health institutes (overall, 2.3%) ($Z = 7.59$, $p < 0.001$).

GI disorders (ICD 9 CM 530–537, 555–558, 560–569) (35.5%) and acute respiratory infections (ICD 9 CM 460–466) (35.1%) were the two major primary diagnostic categories for the 22 175 cisapride prescriptions. However, of the 685 cisapride-erythromycin co-medication episodes, acute respiratory infections (62.8%) was the main primary diagnosis, followed by GI disorders (16.4%), and pneumonia and influenza (4.2%, ICD 9 CM 480–487).

The duration of cisapride-erythromycin co-medication ranged from 1 to 29 days, of which 84.0% of the 464 patients had a co-medication exposure duration in the range of 1–4 days, and 10.8% had an exposure duration of 5–8 days. Of the 464 patients, approximately 81.3%, 11.6%, and 3.0% of them experienced 1, 2, and 5–9 co-medication episodes, respectively in the year 2000.

Characteristics of physicians responsible for the cisapride- erythromycin co-medication

The 22 175 cisapride prescriptions in the LHID 2000 were prescribed by 4240 physicians, of which half (49.1%) were in clinics (Table 4). Excluding the physicians who prescribed cisapride prior to patients being prescribed for erythromycin, a total of 295 cisapride prescribers (7.0% of the total cisapride prescribers of the same year) were considered to be responsible for such cisapride-erythromycin co-medication. There were significant group differences in the rates of cisapride-erythromycin co-medication among four health institutes ($\chi^2 = 30.15$, df = 3, $p < 0.001$). Physicians practicing in the clinics were

Table 3. Cisapride prescriptions and cisapride-erythromycin co-medications in each category of health institute. Data were retrieved from the LHID2000 database

Health institute	Number of cisapride prescriptions (%)	Cisapride-erythromycin co-medication	
		Number	Percentage (95%CI)
Medical centres	2276 (10.3%)	55	2.4(2.0, 2.9)
Regional hospitals	3031 (13.7%)	75	2.5(2.0, 2.9)
Local hospitals	2829 (12.8%)	59	2.1 (1.7, 2.5)
Clinics	14 039 (63.3%)	496	3.5 (3.0, 4.1)
Total	22 175 (100%)	685	3.1 (2.6, 3.6)

Table 4. Number of cisapride prescribers and those who responsible for the co-medication of cisapride and erythromycin in different categories of health institute, based on the LHID2000 database

Health institute	Number (%) of cisapride prescribers	Cisapride prescribers responsible for co-medication	
		Number	Percentage (95%CI)
Medical center	619 (14.6%)	33	5.3 (4.7, 6.0)
Regional hospital	780 (18.4%)	42	5.4 (4.7, 6.1)
Local hospital	759 (17.9%)	28	3.7 (3.1, 4.2)
Clinic	2,082 (49.1%)	192	9.2 (8.4, 10.1)
Total	4,240 (100%)	295	7.0 (6.2, 7.7)

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Table 5. Results of source analysis of cisapride and erythromycin prescriptions for the co-medication episodes.

Health institute	From same doctor		From different doctors	
	From different health institutes	From same health institute	From different health institutes	From same health institute
Medical centres	0	11	20	24
Regional hospitals	0	22	21	32
Local hospitals	0	22	15	22
Clinics	1	366	67	62
Category subtotal	1	421	123	140
Total	685			

more likely to overlook the potential hazard of cisapride-erythromycin co-medication than those in medical centres (OR: 1.73, 95%CI: 1.18, 2.53), regional hospitals (OR: 1.72, 95%CI: 1.21, 2.42), and local hospitals (OR: 2.50, 95%CI: 1.67, 3.75) (Table 4).

Multivariate logistic regression analysis on the characteristics of prescribers responsible for co-medications showed that categories of health institutes and physician's specialty were the statistically significant factors for co-medications. Physicians practicing in clinics that specialized in internal medicine, pediatrics and family medicine significantly increased the likelihood of making such prescribing errors. As depicted in Table 5, it is interesting to note that 61.6% (422 out of 685 episodes) of the co-medication episodes had both cisapride and erythromycin prescriptions prescribed by the same doctors, while 38.4% (263 episodes) had the two drugs prescribed by different doctors practicing at the same institute (20.4%) or different institutes (18.0%). As high as 81.9% (561 out of 685 episodes) of the co-medications were from the same health institute, of which the prescriptions were either from the same or different doctors.

Dosage Analysis for Cisapride Prescriptions

A dosage analysis from the LHID2000 database indicates that 936 prescriptions (4.4%) of 611 patients were prescribed a cisapride dosage higher than 0.8 mg/kg/day, the dose associated with the risk of QT interval prolongation.[9,29,30] Cisapride prescriptions with dosages higher than 0.8 mg/kg/day were mainly from the clinics (710, 75.9%) (Table 6). Most of the over-dosage prescriptions (98.0%) were for patients who were under the age of 16. Furthermore, 11 over-dosage prescriptions (1.2% of 936) for nine patients younger than age 8 were part of the cisapride-erythromycin co-medication episodes. Among these nine patients, seven were exposed to co-medication once and two patients were exposed to co-medication twice. There were no adults who, experiencing such co-medication episodes, were given a cisapride dosage higher than 0.8 mg/kg/day.

Table 6. Distribution of cisapride prescriptions with a cisapride dosage higher than 0.8 mg/kg/day in year 2000 based on LHID2000

Health institute	cisapride dose >0.8 mg/kg/day	
	All cisapride prescriptions	Co-medication cases
Medical centers	48 (5.1%)	0 (0%)
Regional hospitals	83 (8.9%)	1 (9.1%)
Local hospitals	95 (10.1%)	1 (9.1%)
Clinics	710 (75.9%)	9 (81.8%)
Total	936 (100%)	11 (100%)

Clinical consequences of cisapride-erythromycin combination

The 464 patients who were exposed to cisapride-erythromycin co-medication in 2000 were monitored with medical records in the NHI database till the end of 2002. Five patients did not have any claim data or medical records in the NHIRD following co-medication. One 92 year-old patient died of pneumonia 2 years following concomitant drug use. None of the patients receiving cisapride and erythromycin co-medication reported claims for cardiac arrhythmias or other medical events.

DISCUSSION

As this is the first study on the co-medication of cisapride and erythromycin using a national sample in a non-Western country, the major findings of this study were: that the use of cisapride in Taiwan did not

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demonstrate an obvious or continuous decrease of cisapride use since the year 2000, following the alert by Taiwan health authorities in 1999 of the potential of cardiotoxicity; the co-medication of cisapride and erythromycin was observed to be more prevalent in clinics than other medical institutions; and the majority of co-medications (80%) tended to originate from the same institutes and/or same physicians.

Database used

Although the OSD and the LHID2000 subset databases of NHI programme were generated by different sampling methods for different study purposes, they have been demonstrated to be quite reliable. The estimated data for cisapride prescriptions made from clinic settings in 2000 were 62.4% (Table 1) and 63.3% (Table 3) from the two databases, respectively. This finding further supports that the possible errors derived from the databases are not of any significant relevance and therefore, the data used in this study, can be deemed reliable and accurate for the purpose of this study.

Cisapride prescriptions

A drastic reduction of cisapride prescription from 1999 to 2000 was observed internationally, as a consequence of the announcements of cardiac toxicities and drug interactions associated with cisapride.[12,13,16] However, in contrast, despite the persistent alert, there was almost no reduction in cisapride prescriptions for the consecutive 2 years in Taiwan (Figure 2). A lowered reduction rate of cisapride prescriptions was observed in clinics than in hospitals indicating that risk management may be less of a concern to physicians in clinics.

It is not surprising that about 60% of cisapride prescriptions in ambulatory care were from clinics, since 69.9% of patient visits in ambulatory care were from clinics as indicated in the annual report of the BNHI.[31] The NHI programme in Taiwan has literally no restriction for patients on the utilization of health institute resources.[32] While most of the primary physician's visits were made in hospitals, the majority (46.1%) of visits to clinics were for diseases of the respiratory system, of which such claims account for 15.4% of outpatient visits in hospitals in year 2000.[31] However, most of the cisapride usage in ambulatory settings were from the clinics and the complaints of non-specific upper-respiratory infections quite often are accompanied with complaints of GI symptoms. This may be due to the fact that acute respiratory infections (35.1%) as well as GI disorders (35.5%) were the two major primary diagnostic categories for cisapride prescriptions.

Cisapride-erythromycin co-medication

The typical dose of cisapride for adults with GERD is 10–20 mg four times a day, administered 15 min prior to meals and at bedtime.[30] A dose of 5–10 mg, three times a day, is suggested in adults with chronic functional constipation.[33] As only 5 mg- and 10 mg-solid dosage forms are available in Taiwan, most adult patients receive a dose of 5–10 mg, three times a day. Prolongation of the QT interval is more likely to occur when the cisapride dose exceeds 0.8 mg/kg/day in children.[9,29] Reports indicate that patients who experience cardiac toxicities from cisapride use had predisposing risk factors to arrhythmias.[26,34] These risk factors include concomitant use of CYP-450 3A4 inhibitors, previous history of coronary diseases and arrhythmias, renal insufficiency, electrolyte imbalance, and concomitant proarrhythmic drug therapy.[5] However, analysis from this study indicates that patients who experienced cisapride-erythromycin co-medications presented no claims of cardiovascular events. There are several possible explanations for such negative findings. First, the majority of cisapride users, especially those exposed to cisapride-erythromycin co-medication (78.9%), were below the age of 16. The possibility of this population having a previous history of coronary diseases such as arrhythmias, renal insufficiency or electrolyte imbalance would most likely be very low. Second, among the 658 episodes of cisapride-erythromycin co-medications, only 11 episodes (1.6%) (Table 4) of nine patients had a cisapride dosage higher than 0.8 mg/kg/day, the dose reported to have high incidence of the prolongation of the QT interval.[9,29] Third, most of the patients (84.0%) experiencing co-medications were co-medicated for a duration of 1–4 days and most of them (81.3%) had only one co-medication episode where both medications overlapped in exposure. Therefore the incidence of risk after co-medication was probably low for those patients. Unfortunately, we did not have access to the medical records of patients experiencing cisapride-erythromycin co-medications, especially for the five patients who had no claim data in the NHIRD after exposure to the co-medication. Therefore we could not include their data in this study and could not define any conclusive evidence whether there may exist no incidence associated with cisapride-erythromycin co-medication.

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Responsibility of cisapride-erythromycin co-medication

The potential hazard of drug–drug interaction could be easily avoided via proper intra-institutional monitoring mechanisms, which are already available in most of the hospitals in Taiwan. However, there still remains as high as 82%, cisapride-erythromycin co-medications originating from the smaller medical care units in the year 2000. This is probably due to the fact that most of the private clinics are lacking such risk monitoring mechanisms. The same doctors that prescribed both cisapride and erythromycin accounted for 62% of the total co-medication episodes (Table 5). The majority of these doctors (87%) were practicing in clinics, which interestingly, is higher than that of cisapride prescriptions (63%) in clinics from the same population. This trend indicates that not only institutional, but also personal factors play important roles in concomitant prescribing incidences in Taiwan. In view of this, it is imperative to establish more effective procedures to educate physicians in private clinics of updated medication information. Also of interest to know that physicians in clinics are allowed to hire pharmacist to dispense medication inside the clinics in Taiwan. The lack of an effective double-checking mechanism via the separation of dispensing from prescription may also be one of the contributing factors for cisapride-erythromycin co-medication in the clinics.

Limitations

Several methodological limitations should be considered when interpreting the findings in this study. First, the data were retrieved from the medical and pharmacy claim database of the NHI programme. Due to ethical considerations, there was no way to gain access to the medical records of each patient. The findings of this study would be more reliable if they could be validated by the medical records of the patients in this study. Second, the number of diagnoses in the claim data for each medical visit is limited by the BNHI, where a maximum of only three diagnoses for the ambulatory care and five for each inpatient admission were allowed. Combining with this limitation and the lack of medical records, exists the potential hazard of drug co-medication cardiac-related adverse events to be overlooked. Third, comparisons in the reduction of cisapride prescriptions were based on the assumption that the distribution of medical visits in different medical care institutes for ambulatory care were the same during years 1999–2002. This calculation may not be precise. However, the measurement error should be acceptable. Fourth, the dosage calculation may not exactly reflect the true individual dosage situation since patient compliance data was not assessable and patient body weight data was usually not updated in the claim data.

KEY POINTS

- Continuous education about the hazardous co-medication for physicians and pharmacists should be enforced, particularly for those working at clinics.
- A double-checking procedure should be established between prescribing and dispensing to prevent concomitant co-medications.
- Other potential hazardous co-medications should be investigated to prevent possible adverse drug–drug interaction in Taiwan and other developing countries.

CONCLUSIONS

The subsets of NHIRD of National Health Insurance programme in Taiwan provided the database for this pharmacoepidemiology study. Pharmacovigilance can be assessed by analysis from this database. With the cisapride-erythromycin co-medication analysis, the overall prevalence of this co-medication among the cisapride users was 4.5% in Taiwan in the year 2000. There were no cardiac related adverse reactions reported following concomitant use of cisapride and erythromycin as was observed from the data analysis. This negative finding was probably due to the facts that 78.9% of patients experiencing co-medication were under the age of 16, 84.0% of patients experiencing co-medication had short exposure duration (1–4 days) and 98.4% of co-medication episodes had cisapride doses of less than 0.8 mg/kg/day. Physicians in clinics tended to have a higher incidence of such concomitant prescribing behaviour. There is an urgent need in Taiwan, for stricter vigilance of accreditation procedures of clinics and their practicing physicians for the safety of patients and for the prevention of concomitant and contra-indicated prescriptions.

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