

Concurrent Use of Corticosteroids with Licorice-Containing TCM Preparations in Taiwan: A National Health Insurance Database Study

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Abstract

Objectives: This study used a nationwide population-based dataset from the 1997–2003 National Health Insurance claims to explore the prevalence, frequency, and relative risk of concurrent use of systemic corticosteroids with licorice-containing Traditional Chinese Medicine (TCM) preparations that might possibly result in drug–herb interactions.

Design: This study was based on the complete datasets of Western medicine and TCM outpatient reimbursement claims from 1997 to 2003 contained in the National Health Insurance Research Database of Taiwan. According to the date and duration of prescriptions, the patients who concurrently used systemic corticosteroids with licorice-containing TCM preparations were derived for statistical analysis.

Setting: This study was set in Taiwan.

Outcome measures: Descriptive statistics were used to analyze the demographics of patients who used corticosteroids with licorice-containing TCM preparations concurrently, including age, gender, and the frequency and percentage of major diseases in *International Classification of Diseases, 9th version, Clinical Modification (ICD-9-CM)* categories. The relative risk of potential corticosteroid–herb interaction was also analyzed with respect to different characteristics of the patients (age, sexuality etc.).

Results: The prevalence of concurrent use of systemic corticosteroids with licorice-containing TCM preparations through prescriptions from different Chinese medicine and Western medicine physicians was 1.495%. Among the major disease categories, ICD-9-CM codes 280–289 had the highest prevalence rate of 3.803%.

Conclusions: Potential risk of corticosteroid–licorice interactions may happen, even through formal medical services. In the future, such educational propagations should be reinforced. Furthermore, an alert device that includes well-recognized drug–herb interactions should be built into every hospital’s computer system to remind physicians to be cautious on drug safety.

Introduction

CHINESE HERBAL MEDICINE has been widely used for the treatment of a variety of acute and chronic diseases and conditions for thousands of years.¹ Unlike many Western countries, Taiwan has incorporated Traditional Chinese Medicine (TCM) into its national health insurance (NHI) since 1996. People in Taiwan are free to choose Western medicine or TCM, and are allowed to visit either public or private medical facilities.^{2–4} Therefore, it is very common for a patient to take both Western and traditional herbal medicines at the same

time.⁵ Some studies have indicated that the majority of people who use herbal medicine do not reveal this to their physicians or pharmacists.^{6–10}

Besides, recent data have indicated that potentially serious interactions exist between some common herbal medicines and widely used conventional pharmaceuticals.^{1,11–19} Interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either component.¹¹ A number of herb–drug interactions have been identified in humans.²⁰ For example, licorice may potentiate the action of corticosteroids,^{11,21} which has been reported to

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increase the plasma concentration of prednisolone by inhibiting its metabolism,²²⁻²⁴ and promote the vasoconstrictive action of hydrocortisone in the skin.^{1,25}

Licorice has been extensively used as a traditional medicinal herb in China for thousands of years. Licorice as described in the Japanese Pharmacopoeia and Pharmacopoeia of the PRC is the dried roots and stolons (rhizomes) of *Glycyrrhiza glabra* L., *Glycyrrhiza inflata* Bat, or *Glycyrrhiza uralensis* Fisch.^{26,27} The marker compound glycyrrhizin (or glycyrrhizic acid) is hydrolyzed to glycyrrhetic acid in the human body, which is responsible for some of the pharmacological properties associated with preparations made from licorice.²⁸ Licorice has been claimed for therapeutic effects for liver ailments, dyspepsia, gastric ulcers, asthma, bronchitis, rheumatoid arthritis, and has been used as a laxative, anti-tussive, and expectorant medicine.²⁹⁻³¹

Corticosteroids include the adrenal steroid hormone cortisol (hydrocortisone) and related synthetic drugs. They are used to treat autoimmune and inflammatory diseases, including asthma, bursitis, Crohn's disease, tendinitis, ulcerative colitis, rheumatoid arthritis, lupus, and other skin conditions. They are also used to reduce inflammation associated with severe allergic reactions and to prevent transplant rejection.

Moreover, some notable interactions are found to occur between corticosteroids and licorice. Theoretically, glycyrrhizin decreases plasma clearance, increases area under the curves, and increases plasma concentration of prednisolone.^{22,23} The concurrent use of prednisolone with a TCM preparation, *Xaio Chai Hu Tang*, or *Sho-Saiko-To* in Japanese (ingredients include licorice, *Bupleurum falcatum*, *Pinellia ternata*, *Scutellaria baicalensis*, *Zizyphus vulgaris*, *Panax ginseng*, and *Zingiber officinale*) can decrease the blood concentration of prednisolone.²¹ An animal study has shown that glycyrrhizin prevented the immune-suppressing actions of cortisone.³²

Although corticosteroids have been reported to show interactions with licorice, there is no published study examining the prevalence and frequency of concurrent use of corticosteroids with licorice-containing TCM preparations among the Taiwanese.

Therefore, the aim of this study was to use the National Health Insurance Research Database (NHIRD) provided by the Bureau of National Health Insurance for analysis, and a nationwide survey was conducted to establish the frequency of concurrent use of corticosteroids with licorice-containing TCM preparations among patients. In addition, the demographics of the targeted study subjects, the relative risk (RR), and the medical conditions in which patients most commonly combine the use of corticosteroids with licorice-containing TCM preparations were explored for the reference of formulating drug-safety-related strategies.

Materials and Methods

In Taiwan, only outpatient TCM prescriptions are covered by NHI. Inpatients, on the other hand, are excluded from coverage. Therefore, the subjects in this study were limited to Chinese medicine and Western medicine outpatients. The data for this study were extracted from the complete Chinese medicine and Western medicine outpatient claims compiled in the NHIRD provided by the Bureau of NHI. From the database, samples were selected from about 200,000 patients

visiting the outpatient clinics contracted with NHI during the period 1997-2003.

Of the selected samples, those using systemic corticosteroids including hydrocortisone, cortisone, prednisolone, methylprednisolone, dexamethasone, triamcinolone, and betamethasone were screened. Meanwhile, from the datasets of TCM claims, those using licorice-containing TCM preparations were identified. The forms of Chinese herbal medicine covered by NHI were limited to extracted TCM granular and powder preparations prescribed by TCM physicians. Therefore, in this study, only licorice-containing TCM extracted granules or powder were included; crude drugs and other TCM products prepared in traditional methods not covered by NHI were excluded. A total of 128 licorice-containing TCM preparations were analyzed. According to the date and duration of every prescribed corticosteroid and TCM, patients concurrently using corticosteroids with licorice-containing TCM preparations were identified. They were considered for cases that may incur potential corticosteroid-herb interaction and selected for statistical analysis.

SAS Version 9.1 statistical software (SAS Institute, Cary, NC) was used to perform the statistical analysis. Descriptive statistics were used to analyze the demographics of the patients concurrently using corticosteroids with licorice as well as the scale of potential corticosteroid-herb interactions. According to the major disease categories of the *ICD-9-CM [International Classification of Disease, 9th version, Clinical Modification]* a number of data were calculated, including descriptive data, frequency and percentage. Also, based on the variables, such as patient demographics and major disease code, the RR of concurrent use of corticosteroids with licorice-containing TCM preparations was calculated. The RR are presented tighter with their 95% confidence intervals (CI).

Results

A total of 567,647 systemic corticosteroids containing prescriptions were captured in this study. By analyzing the days and duration per prescribed systemic corticosteroids and licorice-containing TCM preparations, the prevalence of concurrent use of corticosteroids and licorice-containing TCM preparations was 1.495%.

The average duration of concurrent use of systemic corticosteroids and licorice was 4.27 days. Dividing the duration into day-specific groups—less than 3 days, 4-6 days, 7-14 days, and longer than 15 days—it was found that the less-than-3-day category had the highest cases of concurrent use of corticosteroids and licorice (Table 1). In regard to age, patients less than 20 years old had the highest percentage of

TABLE 1. DAYS OF CONCURRENT USE OF CORTICOSTEROIDS WITH LICORICE CONTAINING PREPARATIONS

Days	Case no.	Percentage
≤3	6020	70.92%
4-6	1243	14.64%
7-14	959	11.30%
≥15	267	3.15%
Total	8489	100%

TABLE 2. AGE DISTRIBUTION OF CONCURRENT USE OF CORTICOSTEROIDS WITH LICORICE CONTAINING PREPARATIONS

Age (years)	Case no.	Percentage
≤20	1734	20.43%
21–30	889	10.47%
31–40	1430	16.85%
41–50	1434	16.89%
51–60	1071	12.62%
61–70	1124	13.24%
71–80	713	8.40%
≥81	94	1.11%
Total	8489	100%

concurrent use of systemic corticosteroid and licorice-containing TCM preparations (20.43%), and 41–50 years old had the second highest (16.89 %) (Table 2).

By analyzing the percentage distribution of concurrent use of systemic corticosteroid and licorice containing preparations with respect to the major disease categories coded in *ICD-9-CM*, they occurred the most frequently in *ICD-9-CM* codes 460–519 “diseases of the respiratory system” (42.08%), followed by *ICD-9-CM* codes 680–709 “diseases of the skin and subcutaneous tissue” (15.46%) (Table 3).

As for the prevalence rate of concurrent use of systemic corticosteroid and licorice-containing preparations with respect to the major disease categories, *ICD-9-CM* codes 280–289 “diseases of the blood and blood-forming organs” had

the highest prevalence rate of 3.803% (RR=2.8, 95% confidence interval [CI] 2.3–3.3), and *ICD-9-CM* codes 710–739 “diseases of the musculoskeletal system and connective tissue” had the second highest prevalence rate of 3.145% (RR=2.3, 95% CI 2.2–2.4) (Table 4). With respect to sex, “females” had a higher prevalence rate of using systemic corticosteroid concurrently with licorice-containing preparations than the “males,” 1.64% compared to 1.35% (RR=1.2, 95% CI 1.2–1.3). With respect to age, the group of “61–70 years old” had the highest prevalence rate of concurrent use of corticosteroid with licorice-containing preparations (2.08%). Compared with the less than 20-years-old group, the prior group was associated with a 2.5-fold increased risk of current use of corticosteroids with licorice-containing preparations (95% CI, 2.3–2.7; Table 5).

Discussion

Chinese herbal remedies (85.9%) were the most common TCM modality used by this population.² According to Ross et al., 4% of these patients who were prescribed with an oral herbal remedy were also concomitantly prescribed a conventional medicine that had the potential to induce drug-herb interactions.³³ In this study, the prevalence of concurrent use of systemic corticosteroids with licorice-containing TCM preparations was 1.495%. It should be noted that prescribing within the NHIRD represented only a fraction of the total herbal remedy used by patients. Since the data for this study were derived from NHIRD, TCM preparations not covered by NHI were not captured in this study. In other

TABLE 3. COMMON DIAGNOSTIC GROUPS OF CONCURRENT USE OF CORTICOSTEROIDS WITH LICORICE CONTAINING PREPARATIONS

Major disease category	ICD-9-CM code	Case no.	Percentage
Diseases of the respiratory system	460–519	5725	42.08%
Diseases of the skin and subcutaneous tissue	680–709	2103	15.46%
Diseases of the musculoskeletal system and connective tissue	710–739	1723	12.67%
Diseases of the digestive system	520–579	703	5.17%
Diseases of the circulatory system	390–459	616	4.53%
Diseases of the nervous system and sense organs	320–389	612	4.50%
Endocrine, nutritional and metabolic diseases, and immunity disorders	240–279	564	4.15%
Symptoms, signs, and ill-defined conditions	780–799	427	3.14%
Diseases of the genitourinary system	580–629	330	2.43%
Injury and poisoning	800–999	186	1.37%
Infectious and parasitic diseases	001–139	152	1.12%
Mental disorders	290–319	151	1.11%
Neoplasms	140–239	133	0.98%
Diseases of the blood and blood-forming organs	280–289	116	0.85%
Supplementary classification of factors influencing health status and contact with health services	V01–V86	20	0.15%
Supplementary classification of external causes of injury and poisoning	E800–E999	12	0.09%
Congenital anomalies	740–759	9	0.07%
Certain conditions originated from the perinatal period	760–779	3	0.02%
Complications of pregnancy, childbirth, and puerperium	630–677	1	0.01%
Others		18	0.13%
Total		13,604	100%

ICD-9-CM, International Classification of Diseases, 9th version, Clinical Modification.

TABLE 4. THE PREVALENCE AND RELATIVE RISK (RR) OF CONCURRENT USE OF CORTICOSTEROIDS WITH LICORICE CONTAINING PREPARATIONS FOR THE COMMON DIAGNOSTIC GROUPS

Major disease category	ICD-9-CM code	Case no.	Prevalence (%)	RR (95% CI)
Diseases of the respiratory system	460–519	5725	1.366	1 (reference)
Diseases of the skin and subcutaneous tissue	680–709	2103	1.476	1.1* (1.0, 1.1)
Diseases of the musculoskeletal system and connective tissue	710–739	1723	3.145	2.3* (2.2, 2.4)
Diseases of the digestive system	520–579	703	2.253	1.6* (1.5, 1.8)
Diseases of the circulatory system	390–459	616	2.673	2.0* (1.8, 2.1)
Diseases of the nervous system and sense organs	320–389	612	2.239	1.6* (1.5, 1.8)
Endocrine, nutritional and metabolic diseases, and immunity disorders	240–279	564	2.968	2.2* (2.0, 2.4)
Symptoms, signs, and ill-defined conditions	780–799	427	2.099	1.5* (1.4, 1.7)
Diseases of the genitourinary system	580–629	330	2.479	1.8* (1.6, 2.0)
Injury and poisoning	800–999	186	1.600	1.2* (1.0, 1.4)
Infectious and parasitic diseases	001–139	152	1.585	1.2* (1.0, 1.4)
Mental disorders	290–319	151	3.126	2.3* (2.0, 2.7)
Neoplasms	140–239	133	2.319	1.7* (1.4, 2.0)
Diseases of the blood and blood-forming organs	280–289	116	3.803	2.8* (2.3, 3.3)
Supplementary classification of factors influencing health status and contact with health services	V01–V86	20	0.984	0.7 (0.5, 1.1)
Supplementary classification of external causes of injury and poisoning	E800–E999	12	1.232	0.9 (0.5, 1.6)
Congenital anomalies	740–759	9	1.456	1.1 (0.6, 2.0)
Certain conditions originating in the perinatal period	760–779	3	1.471	1.1 (0.4, 3.3)
Complications of pregnancy, childbirth, and the puerperium	630–677	1	0.362	0.3 (0.1, 1.9)
Others		18	1.465	1.1 (0.7, 1.7)

* $p < 0.05$.

ICD-9-CM, International Classification of Diseases, 9th version, Clinical Modification; CI, confidence interval.

words, even if a patient received prescriptions through the formal medical system, and his/her physician had taken the necessary caution, a potential corticosteroids–herb interaction could still happen.

According to the study of Chen et al., analysis on the data derived from Taiwan's NHIRD, female TCM users was higher than male (female:male = 1.13:1).² This study also found that the female had a higher prevalence rate of using corticosteroids concurrently with licorice-containing preparations (1.65%) than the male.

Licorice is widely used in TCM and is a very common ingredient in many TCM preparations. In TCM, licorice is a sweet herb that is commonly used because it has many effects, such as tonifying the heart and spleen, moistening the lungs, relieving spasm, resolving toxic substances, and harmonizing other herbs. The herb is indicated for heart-qi and spleen-qi deficiencies, dryness of the lungs, cough, drug intoxication, swelling of pharynx, toxic sore and other syndromes, and also for relieving spasm, easing pain, and alleviating toxic and drastic properties of other herbs. Fur-

TABLE 5. THE PREVALENCE AND RELATIVE RISK (RR) OF CONCURRENT USE OF CORTICOSTEROIDS WITH LICORICE-CONTAINING PREPARATIONS FOR DEMOGRAPHIC DATA

Category	Cases of using corticosteroids	Cases of concurrent use of corticosteroids with licorice	Prevalence rate (%)	RR (95% CI)
Sex				
Male	280,379	3774	1.35	1 (reference)
Female	285,466	4711	1.65	1.2* (1.2, 1.3)
Age (years)				
≤20	204,324	1734	0.85	1 (reference)
21–30	60,319	889	1.47	1.7* (1.6, 1.9)
31–40	73,062	1430	1.96	2.3* (2.2, 2.5)
41–50	72,658	1434	1.97	2.3* (2.2, 2.5)
51–60	54,362	1071	1.97	2.3* (2.2, 2.5)
61–70	54,066	1124	2.08	2.5* (2.3, 2.7)
71–80	39,017	713	1.83	2.2* (2.0, 2.3)
≥81	9839	94	0.96	1.1 (0.9, 1.4)

* $p < 0.05$.

CI, confidence interval.

thermore, corticosteroids are used to treat autoimmune and inflammatory diseases. Therefore, the major disease category "diseases of the respiratory system" had the highest frequency of concurrent use of corticosteroids with licorice-containing preparations. In this study, it was found that the major disease category "diseases of the blood and blood-forming organs" had the highest prevalence rate of concurrent use of corticosteroids with licorice-containing preparations (3.803%), followed by "diseases of the musculoskeletal system and connective tissue" (3.145%). Therefore, in Taiwan, the prevalence of concurrent use of corticosteroids with licorice-containing preparations not only related to clinical applications, but also to major disease categories.

Since the elderly often suffer from multiple chronic illnesses, concomitant use of multiple medicines is quite common. Consequently, the risk of potential drug–drug interactions or herb–drug interactions is increased.^{1,34} Few studies have examined the incidence of adverse drug reactions, and interactions in the elderly have been reported to be 2–3 times higher than the incidence in younger patients.³⁵ This study showed that those who were "61–70 years old" had the highest prevalence rate of concurrent use of corticosteroid with licorice-containing preparations (2.08%). Compared with patients less than 20 years old, they were associated with a 2.5-fold increased risk of concurrent use of corticosteroids with licorice-containing preparations. The herb–drug interactions are difficult to predict as they depend on a number of factors, including the condition of a patient, dose, and time of administration of drugs and herbs.¹ This study found that the less than 3-day category had the highest cases of concurrent use of corticosteroids and licorice-containing preparations. Because this study was limited to the use of NHIRD, direct access and evaluation of the patient interaction outcome of corticosteroids and licorice-containing preparations interactions could not be performed, nor could the comparison of adverse reactions resulting from different time frames of concurrent use of corticosteroids with licorice.

Conclusions

In addition, based on the findings of this study, further studies are required to examine the impact of corticosteroid–herb interaction for long-term patient outcomes. This study provides information about the prevalence and frequency of concurrent use of corticosteroid with licorice-containing preparations and suggests that potential drug–herb interactions may happen, even through formal medical services. Physicians should examine prescribed drugs and herbal formulations/products to identify whether any ingredients of concern are involved.¹ They should also monitor the patients for any changes in the efficacy or worsening of side-effects of the administered drugs after patients have started taking herbal medicines at the same time.

In the future, it is suggested that an alert database that contains well-recognized drug–herb interactions be built in the computer system of every hospital to remind physicians to take caution on drug safety and monitor potential herb–drug interactions while prescribing medicine. An alert database is a useful mechanism in hospitals. If a doctor want to prescribe two drugs that have known interactions, the system will prompt a signal to remind the doctors of

this possible interaction to reduce drug–drug interaction cases. If we have more evidence of herbs and drug interactions, we can also put it in the system to remind the doctors to avoid using such drugs together.

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Disclosure Statement

No competing financial interests exist.

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