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DRUGS AND THE LIVER

Utilization of hepatoprotectants within the National Health Insurance in Taiwan

TZENG-JI CHEN,* LI-FANG CHOU† AND SHINN-JANG HWANG*

**Department of Family Medicine, Taipei Veterans General Hospital and National Yang-Ming University School of Medicine and †Department of Public Finance, National Chengchi University, Taipei, Taiwan*

Abstract

Background and Aims: Although the hepatoprotectants of Western medicine have centuries of history, their utilization patterns have been seldom documented. Because the National Health Insurance program in Taiwan reimburses hepatoprotectant use, we could estimate the age- and sex-specific prevalence and utilization patterns of hepatoprotectants in Western medicine within the health insurance system in Taiwan.

Methods: We analyzed the outpatient prescription data of 50 000 randomly sampled insured patients in 2000. Only patients using drugs indicated for liver diseases and diagnostic codes related to liver diseases on the same visit were considered to be receiving hepatoprotectants. Drugs involved in Chinese medicine were not included.

Results: Among the valid cohort of 46 614 people, 783 (1.7%) were identified as patients with liver disease and receiving hepatoprotectants. Highest prevalence of hepatoprotectant use was 4.9% in the 60–69 years age group. Silymarin, multivitamins, methionine, ursodeoxycholic acid, and liver hydrolysate accounted for 88.8% of the 3215 prescribed items of hepatoprotectants. Patients receiving hepatoprotectants had, on average, visited the clinics more frequently than those not using hepatoprotectants (30 *vs* 14 times in a year, $P < 0.001$), and used more insurance benefits (US$1352 *vs* US$456, $P < 0.001$).

Conclusions: The frequency of use of major hepatoprotectants in Taiwan corresponded to the current modalities of treatment under discussion worldwide.

Key words: drug utilization, liver diseases, national health programs, pharmacoepidemiology, protective agents.

INTRODUCTION

While modern medicine pays close attention to corticosteroids, interferons, and other antiviral agents in treating liver diseases, the traditional remedies, also known as hepatoprotectants, are still very popular worldwide.[1–6] Although the Anatomical Therapeutic Chemical (ATC) classification system for drugs[7] recognized by the World Health Organization (WHO) includes a subgroup of drugs for liver therapy (A05BA), some important national formularies such as the BNF (British National Formulary)[8] do not mention any hepatoprotectants, apparently considering these types of drugs as naturopathic. Because most health insurance or public health services worldwide do not pay for diverse therapies outside the mainstream of 'official' medicine, the utilization patterns of hepatoprotectants has been seldom documented.

Taiwan, an island situated in south-east Asia and with a population of more than 22 million, is hyperendemic for viral hepatitis.[9–12] The National Health Insurance (NHI) program in Taiwan not only offers the services of traditional Chinese medicine in treating patients with liver diseases but also reimburses the hepatoprotectants prescribed in Western medicine. In the current study, we analyzed NHI claims in Taiwan to estimate the age- and sex-specific prevalence of hepatoprotectant (of Western medicine) use within the health insurance system. The strength of our study lied in the use of a longitudinal dataset of a representative cohort.

Correspondence: Professor SJ Hwang, Department of Family Medicine, Taipei Veterans General Hospital, No. 201, Section 2, Shih-Pai Road, Taipei 11217, Taiwan. Email: sjhwang@vghtpe.gov.tw

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It was proposed a survey of insurance benefits use would help to understand the health condition of Taiwan's population and the current trend of hepatoprotectant use.

METHODS

Data sources

The NHI program in Taiwan has been implemented since 1995 and covered more than 96% of the population at the end of 2000 (21 400 826 insured out of 22 276 672 inhabitants[13]). The NHI offers the inpatient and outpatient services of Western medicine, dental medicine and traditional Chinese medicine.

We obtained the first cohort dataset from the National Health Insurance Research Database (NHIRD). The cohort included 50 000 people randomly sampled from 23 753 407 people who had ever been insured under the NHI since 1995. The dataset contained all claims data of these individuals. In the current study, we analyzed only the outpatient visit and prescription files of the cohort dataset in 2000. Also, we obtained a complete file of 21 146 approved drug items used in Western medicine in Taiwan from the Bureau of NHI. Each drug of a different brand, strength, form, and manufacturing country was officially assigned a unique 10-digit code that was used in the claims file. The Bureau of NHI also offered a list of ATC codes (4th level) for each drug.

Study design

The NHI in Taiwan reimbursed the hepatoprotectants used in Western medicine only on the condition of clinically evident hepatitis, liver cirrhosis, and abnormal liver function with an elevated serum alanine or asparate aminotransferase level above the upper normal limit in the recent three months. The prescribing physician documented the laboratory values and any violation could have resulted in a fine up to 100 times the price of prescribed drugs. Such a rigid restriction implicitly validated the diagnosis of liver diseases. Therefore, we initially identified the patients receiving hepatoprotectants through the drugs prescribed at the outpatient clinics for Western medicine. We did not confine our search to the drugs in the ATC subgroup for liver therapy (A05BA), which included only six chemical ingredients (arginine glutamate, silymarin, citiolone, epomediol, ornithine oxoglurate, and tidiacic arginine). To reflect the current modalities in treating liver diseases, six additional groups of drugs were recruited:

- ATC subgroup for bile acid preparations (A05AA), mainly ursodeoxycholic acid
- ATC subgroup for various alimentary tract and metabolism products (A16AX), especially tioctic acid
- ATC subgroup for vitamin B12 and folic acid (B03B)
- ATC subgroup for solutions for parenteral nutrition (B05BA)
- ATC subgroup for antidotes (V03AB), especially methionine and glutathione
- Other drug items with an officially approved indication of liver disease

Because a drug might not be limited to one indication only, we refined our search with the claims diagnoses in accordance with International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) coding. Only patients on hepatoprotectants with ICD-9-CM codes of 070, 155, 570–3, 789.1, 790.4, 794.8, V02.6, and V10.07 on the same visit were considered to be receiving hepatoprotectants.

After identifying the patients, we computed the age- and sex-specific prevalence of liver therapy. The denominators were those people who were still insured under the NHI in 2000. Patterns of drug items were also calculated. Comparisons were made between patients using hepatoprotectants and insured patients not using hepatoprotectants, where the estimates were the average outpatient visit count and medical care expenses.

Data processing and statistical analysis

Database software (Microsoft SQL Server 2000) was used for data linkage and processing, while SPSS for Windows, (SPSS Inc., Chicago, IL, USA) was used in the analyses. Univariate comparisons were tested using Student's *t*-test for continuous variables. A *P*-value of less than 0.05 (two-tailed test) was considered statistically significant.

RESULTS

Among 50 000 people in the cohort dataset, only 46 614 were still insured under the NHI in 2000 and 42 753 (92.8%) had used the medical care services reimbursed by the NHI during the entire year. The 46 614 people served as the denominator for calculating the prevalence, and their age-sex distribution did not differ significantly from that of the general population in Taiwan (Table 1). In total, 783 people were identified as patients with liver disease and receiving hepatoprotectants. Overall prevalence of liver therapy was 1.7%. No patients in the 0–9 years age group had received hepatoprotectants. Prevalence of hepatoprotectant use increased gradually from 0.2% in the 10–19 years age group to 4.9% in the 60–69 years age group before declining a little in the 70+ years age group. The male to female ratio in the prevalence of liver therapy was 1.6 (2.1 to 1.3%) and women only had a higher rate than men in the 60–69 years age group.

Hepatoprotectants or drugs indicated for liver diseases had been prescribed during 3156 outpatient visits by these 783 patients. Prescription items amounted to 3215 and consisted of 88 different drug items with 13 main ingredients. Table 2 lists the frequency of substances used as hepatoprotectants. Silymarin (plain preparation and combinations) was the most popular ingredient and had a share of more than one-third

Table 1 Age-sex distribution of general population in Taiwan, sampling cohort, and patients receiving liver therapy

Age (years)	General population[15]			Sampling cohort†			Patients receiving liver therapy			Prevalence of liver therapy (%)		
	Total	M	F	Total	M	F	Total	M	F	Total	M	F
0–9	3 104 400 (13.9)	1 618 471	1 485 929	6 486 (13.9)	3 368	3 118	0 (0.0)	0	0	0.0	0.0	0.0
10–19	3 474 056 (15.6)	1 796 028	1 678 028	7 106 (15.2)	3 587	3 518	17 (2.2)	12	5	0.2	0.3	0.1
20–29	3 780 665 (17.0)	1 929 074	1 851 591	8 116 (17.4)	4 028	4 088	53 (6.8)	41	12	0.7	1.0	0.3
30–39	3 828 978 (17.2)	1 947 241	1 881 737	8 075 (17.3)	4 104	3 971	134 (17.1)	106	28	1.7	2.6	0.7
40–49	3 484 626 (15.6)	1 760 966	1 723 660	7 179 (15.4)	3 530	3 649	184 (23.5)	123	61	2.6	3.5	1.7
50–59	1 914 115 (8.6)	956 506	957 609	3 920 (8.4)	1 920	2 000	152 (19.4)	78	74	3.9	4.1	3.7
60–69	1 427 566 (6.4)	706 132	721 434	3 014 (6.5)	1 493	1 521	148 (18.9)	73	75	4.9	4.9	4.9
> 70	1 262 266 (5.7)	677 632	584 634	2 718 (5.8)	1 468	1 250	95 (12.1)	55	40	3.5	3.7	3.2
Total	22 276 672 (100.0)	11 392 050	10 884 622	46 614 (100.0)	23 498	23 115	783 (100.0)	488	295	1.7	2.1	1.3

† Status of sex was unknown in one insured; values in parentheses are percentages.

Table 2 Frequency of major chemical substances used for liver therapy

Main ingredient	Preparation form	No. prescriptions (%)
Silymarin	Combination	627 (19.5)
Silymarin	Plain	490 (15.2)
Multivitamins	Combination	581 (18.1)
Methionine	Combination	562 (17.5)
Ursodeoxycholic acid	Plain	367 (11.4)
Liver hydrolysate	Combination	229 (7.1)
Ornithine	Plain	175 (5.4)
Ornithine	Combination	38 (1.2)
Vitamin B_{12}	Plain	51 (1.6)
Vitimin B_{12}	Combination	8 (0.2)
Betaine	Combination	41 (1.3)
Folic acid	Plain	22 (0.7)
Thioctic acid	Combination	9 (0.3)
Thioctic acid	Plain	5 (0.2)
Arginine	Combination	7 (0.2)
Diisopropylamine	Plain	2 (0.1)
Tiopronin	Plain	1 (0.0)
Total	—	3215 (100.0)

(34.7%). Multivitamins were the second most popular (18.1%), followed by methionine (17.5%), ursodeoxycholic acid (11.4%) and liver hydrolysate (7.1%). These five groups of drugs accounted for 88.8% of the prescription items of hepatoprotectants already.

As shown in Table 3, we compared the 783 patients receiving hepatoprotectants with those (45 831) not receiving them. On average, patients receiving hepatoprotectants visited the clinics more frequently than those not using them (30 *vs* 14 times per year, $P < 0.001$). There were no significant differences in each age group. Correspondingly, patients receiving hepatoprotectants had used more insurance benefits, including outpatient, inpatient, and pharmacy services than those not using hepatoprotectants (US$1352 *vs* US$456, $P < 0.001$), but the difference in the 10–19 years age group was not statistically significant.

DISCUSSION

To the best of our knowledge, the statutory health insurance system in Germany also reimburses hepatoprotectant use and has published the yearly nationwide use since the 1980s.[14] While German statistics regarding hepatoprotectant use came from prescription-based sampling and showed only the total use, the person-based sampling in our study could estimate the prevalence of hepatoprotectant use in the population.

The hepatoprotectants of Western medicine in our study did not include interferons and antivirals such as lamivudine or ribavirin that had not yet been reimbursed by the NHI in Taiwan. Therefore, the prevalence of patients treated for liver disease would undoubtedly

Table 3 Difference in the average outpatient visit frequency and total medical expenses between patients receiving hepatoprotectants and insured patients not using hepatoprotectants

	No. outpatient visits in 2000					Total medical expenses in 2000 (US$)†				
	Using hepatoprotectants ($n = 783$)		Insured, not using hepatoprotectants ($n = 45\,831$)‡			Using hepatoprotectants ($n = 783$)		Insured, not using hepatoprotectants ($n = 45\,831$)‡		
Age (years)	Mean§	SD	Mean	SD	*P*-value⋆	Mean¶	SD	Mean	SD	*P*-value⋆
0–9	—	—	20	14	—	—	—	326	883	—
10–19	21	9	9	8	< 0.001	461	347	201	926	0.246
20–29	18	14	9	10	< 0.001	619	832	252	650	0.002
30–39	24	19	11	11	< 0.001	783	1350	328	974	< 0.001
40–49	25	14	13	13	< 0.001	1106	2072	418	1218	< 0.001
50–59	29	18	17	15	< 0.001	1250	1945	698	2058	0.001
60–69	38	21	21	18	< 0.001	1606	1871	1031	2455	0.005
> = 70	43	23	26	22	< 0.001	2970	4208	1543	3248	0.001
Total	30	20	14	14	< 0.001	1352	2310	456	1478	< 0.001

† Original expenses have been converted into US$, based on the exchange rate on December 30, 2000 (US$1 = 32.9920 New Taiwan Dollars); ‡ Includes the insured who did not use any insurance benefits; § includes all kinds of visits by a patient, not limited to visits on which liver therapy occurred; ¶ includes all kinds of expenses by a patient, not limited to expenses for liver therapy; ⋆Student's *t*-test.

be underestimated in our study. Most hepatoprotectants were not prescription-only and self-medication could not be ascertained. Also, hepatoprotectants used in traditional Chinese medicine were not calculated at the same time in our study. The drugs of Chinese medicine (mostly herbal ingredients) reimbursed by the NHI in Taiwan included industrially manufactured preparations and extemporaneously compounded products. Traditional Chinese medicine has its own logical system and currently lacks a standardized drug classification system. The study of hepatoprotectant use in traditional Chinese medicine is thus beyond the scope of our current study.

The most important justification for initiating and continuing hepatoprotectant prescription to the NHI insured in Taiwan was the biochemical proof of abnormal liver function in the last three months. However, abnormal liver function was not specific for certain diseases or stages of illnesses. In our study, we did not differentiate between acute or chronic hepatitis, liver cirrhosis, and primary hepatocellular carcinoma. Conversely, although the serum alanine or asparate aminotransferase level did change with aging, this was usually slight and insignificant.[15,16] Hence, the high prevalence of hepatoprotectant use in the older age groups might be better explained by the high prevalence of liver diseases.

The frequency of major chemical substances used for treating liver diseases in Taiwan revealed the current mode of treatment. Silymarin, a derivative of milk thistle (*Silybum marianum*), has a history of almost 2000 years in the Occident as a herbal remedy and has been the focus of attention recently.[17] It is also popular in Taiwan. Although methionine and ursodeoxycholic acid were not classified under the ATC subgroup for liver therapy (A05BA), their extensive use as hepatoprotectants in Taiwan followed the current academic opinions worldwide.[18–22] The role of multivitamins in treating liver diseases remains unknown.

Our results reveal that the patients receiving hepatoprotectants visited the clinics more frequently and consumed more medical care resources than the other insured patients. The insured patients not using hepatoprotectants were heterogeneous and included those who did not use any insurance benefits in the entire year (7.2%). Further analyses are required to see how the patients using hepatoprotectants differ from other risk groups (e.g. patients with cardiovascular and metabolite disorders) in medical care utilization.

In conclusion, we performed only a descriptive study. Further studies are needed to investigate whether the hepatoprotectants are 'mass placebos' or effective alternatives in the treatment of liver diseases.

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