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Doctor thesis

# 肝毒性藥物的流行病學研究

# Epidemiologic study of hepatoxic medications

李長興

Lee, Chang-Hsing

指導教授：陳保中 王榮德 博士

Advisors: Chen, Pau-Chung Wang, Jung-Der Ph.D.

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| 備註 | | | | | | | | | |

# 誌謝

又是一個寂靜的午夜，開始跑資料後，似乎都習慣了這樣的深夜。完成了這篇論文，感覺有些如釋重負，但依稀又是另一個沈重負荷的開始，很五味雜陳，對中醫，對自己。

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父母無怨尤的支持，才有今天我的小小進步。

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博士畢業，是另一個研究生涯的開始！

# 中文摘要

**背景：**儘管草藥產品日益受到歡迎， 中藥所造成肝傷害的潛在危害越來越受到關注。此外，肝毒性案例報告有關新的藥物(nimesulide, celecoxib and rofecoxib)逐漸增加。在台灣病毒肝炎的盛行率是非常高的。台灣健保資料庫提供了一個機會進行藥物的上市後監測。藥物造成肝的不良反應的流行病學過去很少有相關研究，也因為難以進行研究。因此，我們對於中藥及可能造成肝毒性的新藥及台灣國民的肝傷害間的關係的流行病學研究感到興趣。因此，我們進行研究的三個目標：(1) 我們進行了觀察性研究，評估是否病例對照研究和病例交叉研究設計(case-control and case-crossover designs)，利用電腦資料庫，可用於檢測出肝毒性藥物在肝損傷的風險;(2) 研究台灣國民使用中藥與急性肝炎住院的關係;(3) 研究台灣國民使用止痛新藥 cyclo-oxygenase-2 (COX-2) selective inhibitors 與急性肝炎住院的關係。

**方法：**第一個研究設計：研究材料是使用大約 2200 萬多人參加的，從 1997 年 1 月 1 日至 2004 年 12 月 31 的台灣全民健康保險資料庫。我們採用病例對照研究和病例交叉設計，來對已知的肝毒性藥物 isoniazid, rifampicin, erythromycin 及 diclofenac 所造成的肝傷害進行.風險評估。我們使用上述兩個研究設計，並使用調整其他肝毒性藥物使用及共同疾病的 Logistic 回歸模型來統計。第二個研究設計：使用 1997 至 2002 年 20 萬隨機抽樣歸人檔的健保研究資料庫，進行病例交叉研究(case-crossover design)。採取在住院前的 30 及 60 天期間的所有藥物進行了探討，並與四個控制時期（住院之前及之後的 180 和 360 天）。進行在危險期間的中藥處方的勝算比的 logistic 回歸模型研究。第三個研究設計：研究新藥與傳統肝毒性非固醇類止痛藥造成急性肝炎之間的關係，設計單邊與雙邊的 28 天暴露期間的病例交叉研究兩種模型，並使用 logistic 回歸模型統計。

**結果和結論：**第一，病例對照及病例交叉研究兩種研究設計，所得到肝傷害

住院病人在住院前 30 天的暴露肝毒性藥物的矯正後勝算比是相近且顯著增加的。使用健保資料庫，兩個研究設計都可以使用來評估肝毒性藥物造成的肝傷害風險。第二，在非病毒，非酒精性急性肝炎的族群，在矯正過傳統肝毒性西藥後，中草藥使用顯示略有增加急性肝炎的風險。因此，我們建議對可能肝毒性的中藥使用，進行藥物主動監視。第三，celecoxib, nimesulide, dicofenac, ibuprofen 和其他肝毒性非固醇類止痛藥的勝算比是顯著增加的。我們的結果對肝毒性非固醇類止痛藥包括 celecoxib 使用，造成急性肝炎住院風險增加，提供證據。進一步的機轉研究來證實 celecoxib 的肝毒性是必要的。

# Table of content

# Abstract

**Background**: Despite the increase in popularity of herbal products, there is growing concern over potential hepatoxic hazards caused by the Chinese herbal medicines (CHMs). Otherwise, case reports of hepatoxicity about new drugs (nimesulide, celecoxib and rofecoxib) seem to increase. The prevalence rates of viral hepatitis are very high in Taiwan. The reimbursement database of National Health Insurance (NHI) in Taiwan provided an opportunity for post-marketing surveillance. The epidemiology of adverse hepatic reaction remains poorly documented and hard to conduct. Our epidemiologic studies were interested in an attempt to determine the association between the use of CHMs or potential hepatoxic new drug and the risk of liver injury amongst the citizens of Taiwan. Thus, we conducted our study for three objectives; (1) our observational study was conducted to assess if case-control and case-crossover designs could be applied to detect the risk of hepatoxic drugs on liver injury in the automated databases.; (2) to determine the association between the use of CHMs and the risk of hospitalizations related to acute hepatitis amongst the citizens of Taiwan; (3) to determine the association between the use of cyclo-oxygenase-2 (COX-2) selective inhibitors and the increased hospitalizations related to liver injury among the citizens of Taiwan.

**Methods:** First design: the study was conducted on approximately 22 million people enrolled in Taiwan's national health insurance database from January 1, 1997 to December 31, 2004. We applied case-control and case-crossover designs to assess the estimated risks of liver injury related to well-known hepatoxic drugs, including isoniazid, rifampicin, erythromycin, and diclofenac.

We applied two designs by conditional logistic regression model to adjust for other hepatoxic drugs and co-morbidity. Second design: a case-crossover study was designed on 200,000 randomly selected individuals from the NHI Research Database who were then followed from 1997 to 2002. All medications taken in the 30- and 60-day periods prior to hospitalization were explored and compared with four control periods (the 180- and 360-day periods prior to and after the hospitalization). A conditional logistic regression model was then constructed to determine the odds of CHM being prescribed during these risk periods. Third design: we conducted to determine the association between the use of hepatoxic NSAIDs and increased hospitalizations related to acute hepatitis. We applied two kinds of models to analyze by uni-directional and bi-directional case-crossover designs during the 28 days exposure periods and performed conditional logistic regression models.

**Results and conclusions:** First, the adjusted odds ratios of hospitalized liver injury patients during the 30-day exposure window showed similar and significant increases for hepatoxic drugs by the case-control and case-crossover designs. The risk of admission with liver injury related to hepatoxic drugs could be assessed by both designs based on automated databases. Second, after adjustment for conventional hepatotoxic drugs, Chinese herbal users revealed a slightly increased risk of acute hepatitis for nonviral, nonalcoholic acute hepatitis. We therefore recommend active surveillance for CHMs suspected with hepatotoxicity. Third, the odds ratios of celecoxib, nimesulide, dicofenac, ibuprofen and other hepatoxic NSAIDs were significantly increased. Our results provide evidence for an increased risk of hospitalization with acute hepatitis among hepatoxic NSAIDs including

celecoxib users. Further mechanistic research is warranted in order to document celecoxib's hepatotoxicity.

# Chapter Ⅰ background

### Drug-induced liver injury (DILI)

Since the liver is central to the biotransformation of all drugs and foreign substances, drug-induced liver injury is a potential complication of nearly every medication that is prescribed. The liver is the most common target organ for toxicity encountered during the course of drug development. (1) The toxic effects of drugs on the liver have remained ignored or, at least, underestimated for a long time. The hepatotoxicity of herbal medicines in Western countries has been recognized for about 10 yr.(2)

Drug-induced liver injury represents a clinical challenge owing to the large number of reported hepatoxic drugs in current use, the different kinds of hepatic injury and the frequent absence of clinical findings. Injury induced by complementary and alternative medications has become more common as the use of these medications has increased. Establishing a definitive diagnosis of drug-induced liver injury remains, to date, usually difficult in most cases. (Table 1) (3)

**Table 1 Major difficulty in the diagnosis of drug-induced hepatitis**

| |
|---|
| Nonspecific clinical features |
| Treated disease itself leading to liver abnormalities (bacterial infection) |
| Intake of several hepatoxic drugs (combined antituberculosis agents) |
| Compounds considered safe (herbal remedies) |
| Drug prescription difficult to analyze: |

automedication
masked information (illegal compounds)
forgotten information (elderly)
Fulminate hepatitis

In the last 20 yr, several analytical methods have been proposed to assess the causality of a given drug in the occurrence of liver injury. In 1990, an international consensus group proposed definitions of adverse reactions and criteria for assessing causality of DILI liver diseases to standardize the evaluation of drug hepatotoxicity by physicians, health authorities of different countries and pharmaceutical manufacturers. (4) The possibility of a drug reaction must be considered in any patient with liver dysfunction. A careful drug history should be taken, which includes the patient's use of prescription, over-the-counter, herbal, or alternative medications. Other causes of liver dysfunction, such as viral hepatitis, hypotension, and biliary tract or liver disease related to alcohol abuse, must be excluded by a thorough medical history taking, ultrasonography, and appropriate serologic tests.(3)

Table 2 Diagnostic criteria

| |
|---|
| **Chronological criteria** |
| Interval between the beginning of the treatment and the onset of liver injury: 1 week-3 months |
| Regression of liver abnormalities after withdrawal of the treatment |
| Relapse of liver abnormalities after accidental readministration of the offending drug |
| **Clinical criteria** |
| *Elimination of other causes* |
| Previous hepatic or biliary disease |
| Alcohol abuse |
| Viral hepatitis (HAV, HBV, HCV, HDV CMV, Epstein-Barr virus, Herpes |
| Biliary obstruction (ultrasonography etc.) |

| |
|---|
| Autoimmune hepatitis/cholangitis |
| Liver ischemia |
| Wilson’s disease |
| Bacterial infection (Listeria, Campylobacter, Salmonella) |
| *Positive clinical criteria* |
| Age >50 yr |
| Intake of many drugs |
| Intake of a known hepatoxic agent |
| Specific serum autoantibodies: anti M6, anti LKM2, anti CYP lA2, anti CYP 2El |
| Drug analysis in blood: paracetamol, vitamin A |
| Liver biopsy: microvesicular steatosis, eosinophil infiltration, centrilobular necrosis |

The epidemiology of adverse hepatic reaction remains poorly documented. Drug toxicities cause most cases of liver failure in the United States, (5) and liver damage is a major reason for withdrawal of a drug from the market. (6) In France, the incidence rate of outpatient drug-induced liver injury amounts to 14 cases per 100,000 inhabitants, which is still considered as an underestimation because of difficulty in diagnosis.(7) Given such a relatively rare incidence, DILI usually may not be detected in clinical trials with limited numbers of subjects. Therefore, increasing cases of hepatotoxicity may emerge after starting marketing when a sufficient number of patients have been exposed to the new drug. (8)

**Hepatotoxicity of Chinese herb medicines (CHMs)**

Chinese herbal remedies have been used extensively as a means of treating various illnesses, among communities in China, Japan, Korea and Taiwan, for thousands of years. Since most of these medications are derived from herbs, there is often a perception among the regular users of these remedies that they are gentle and nontoxic; (9, 10) and indeed, there has been

a reported increase in the overall consumption of herbs or herbal medicines, over the past two decades. The use of herbal medicine in the United States has risen from 2.5% in 1990 to 12.1% in 1997 (11) and 9.6% in 1999. (12)

Nevertheless, the Poison and Drug Center data collection program in Taiwan has recorded over 100 cases of poisoning following the consumption of herbs by individuals. (13) In addition to the infamous nephrotoxic events of herbs with aristolochic acid, an increasing number of herbal remedies are now being reported as hepatoxic, (14) with such reports on CHMs including a variety of groups, such as *Radix Scutellariae*, *Radix Bupleuri*,(15) *Herba Ephedrae*, (16) *Radix Polygoni Multiflori,*(17) *Atractylodis macrocephalae. rhizoma*, *Radix Glycyrrhizae*,(18) *Radix Paeoniae*, *Cortex Moutan*, and *Cortex Dictamni.*(19)

Most of these reports of poisonings were case reports, and not epidemiological studies; and indeed there have been relatively few epidemiological studies which have addressed the relationship between CHMs and worldwide hepatic adverse effects. Therefore, many cases of herbal-related toxic hepatitis may continue to go unrecognized and unreported. (20)

**Hepatotoxicity of new drugs**

Cyclo-oxygenase-2 selective (COX-2) inhibitors were developed for the treatment of chronic osteoarthritis and rheumatic arthritis and considered to be free from gastrointestinal side effects. Recently, case reports related to hepatoxicity seem to increase for nimesulide,(21, 22, 23) celecoxib,(24, 25, 26, 27) and rofecoxib.(28, 29) However, a meta-analysis of clinical trials concluded that celecoxib has a low hepatotoxicity.(30) Another cohort study(31) and a

case/non-case analysis (32) seemed to result in the same conclusion. In Taiwan, national reporting center of adverse drug reactions analyzed the 53 passive reports about adverse effects of COX-2 inhibitors during 1999 to 2004. They found rofecoxib leads to an admission with the diagnosis of acute hepatitis and the other case with liver dysfunction related to nimesulide.(33) Because most studies of post-marketing surveillance relied mainly on passive reporting system, they could have under-estimated the true figures. Is there any hepatoxic risk when these new drugs had been taken by the patients in Taiwan?

**Viral hepatitis and hepatoxic medicines**

The prevalence rates of viral hepatitis are very high in Taiwan; more than 90% of the general population having contacted hepatitis B virus (HBV) infection; and the prevalence of chronic infections is as high as 15–20%. Furthermore, the seroprevalence of the hepatitis C virus (HCV) amongst the general population has also been reported at 2–3%. (34)

Is the patient with liver disease more susceptible than others to liver injury? If liver function is impaired, one might expect a diminished likelihood of toxic reactions as a result of decreased enzyme activity. For example, patients with hepatitis C do appear to be at increased risk for veno-occlusive disease after myeloablative therapy in preparation for bone marrow transplantation. (35)

A study undertaken in the US found that 39% of liver disease patients had used some form of complementary/alternative medicine (CAM) prior to their diagnosis, and that the CAM used by 21% of these patients was some form of herbal medication, thereby raising concerns of potential

hepatotoxicity.(36)

Is there more or less risk when hepatoxic drugs or Chinese herbs had been taken by the patients with viral hepatitis B and C?

**The database of National Health Insurance**

The National Health Insurance (NHI) program in Taiwan is a universal system of compulsory health insurance, which was implemented on 1 March 1995 and which has been providing coverage for 96.2% of the population of Taiwan and the proportions of contracted medical care institutions are about 96.5% of all hospitals and 89.5% of all clinics since the end of 2000. (37)

The importance of the National Health Insurance database cannot be underestimated, since, not only does it contain virtually all of the health insurance medical records for all citizens in Taiwan, but it is possibly the most comprehensive record of CHM users available anywhere in the world.

For all medical care institutions contracted under the NHI system, the Taiwanese government reimburses not only general healthcare expenditure, but also the costs of prescriptions for CHMs. Since all of these claims for reimbursement must be submitted in computerized form, the availability of such data reveals that outpatient CHM accounts for 9% of all medications consumed in terms of frequency of use. These figures clearly indicate the important role played by CHM in the Taiwanese healthcare system, with the CHM prescriptions covered by the NHI including virtually all of the popular CHMs (amounting to 780 different kinds of single herbs and mixed formulae) in concentrated extract form.(38) This computerized database of CHMs provides us with an invaluable opportunity to undertake a population-based study. Following payment of only a small fee, patients can take the CHM prescriptions

provided to them by doctors practicing CHM. The further use of this computerized database, of which this study represents one such trial, is strongly recommended, since we believe that it can provide extensive information for the safe use of CHMs.

Otherwise, The NHI database contains virtually all of the health insurance medical and prescription records for almost all citizens in Taiwan, which provides an opportunity for post-marketing surveillance of potential hepatoxic drugs.

**Case-crossover design**

In this design only cases that have experienced an outcome event are considered. The `controls' are the same cases at earlier times, hence the name case-crossover. It can then be determined whether or not, cases were either exposed or not exposed to the drug under consideration, either at event time or `control-time'. Control selection bias is eliminated as the cases act as their own controls. There is also a saving in resources since there is no need to collect information on a separate group of controls and, in addition, it is not necessary to collect information from the cases on time-constant factors. The design resembles a retrospective cohort study with crossover between exposure and non-exposure. It also resembles an experimental crossover design, except that the order of exposure is not randomized. It is immediately obvious that the design is not suitable for studying drug safety for chronic conditions, which require constant medication. Its strength lies in eliminating control selection bias and its main potential in pharmacoepidemiology lies in assessing acute transient events following intermittent drug exposure. There have been relatively few pharmacoepidemioloigic studies carried out using

case-crossover design. (39)

Case-control design is a suitable choice for studying rare diseases, including adverse drug reaction. (40) However, there may be potential confounders that have not been recorded in the automated databases used for analysis. In 1991, Maclure proposed the case-crossover design, which can deal with this problem as a means of controlling for factors within subjects. (41) Therefore, our observational study was conducted to assess if these designs could be applied to detect the risk of hepatoxic drugs on liver injury. Moreover, we estimated the risk in different exposure windows by sensitivity analysis,(42) because the latent period of DILI may vary widely among individuals. (8)

**Main objective**

Our epidemiologic studies were conducted in an attempt to determine the association between the use of medications and the risk of CHMs-or hepatoxic drug- induced liver injury amongst the citizens of Taiwan.

**研究假說形成背景**

1. 健保給付藥物種類 13000 多種,加上 780 種中藥,種類繁多.藥物引起肝傷害(Drug-induced liver injury)為美國肝衰竭最常見原因. 國際上中藥引起肝傷害的個案報告逐漸增加,國內中藥引起肝傷害的流行病學狀態如何?另外西藥的止痛新藥,COX-2 selective inhibitors(celecoxib, rofecoxib, nimesulid)引起肝傷害個案報告逐漸增加,但 metaanalysis,case/noncase 分析顯示 celecoxib 的肝毒性風險極低,台灣使用的肝毒性風險有是如此?
2. 台灣為病毒性肝炎的高盛行率地區,藥物在病毒性肝炎族群引起之肝傷害風險如何?
3. 藥物引起肝傷害為一發生率約為 1/10,000 之罕見疾病,需大量樣本數之族群才適合研究,約有 22,900,000 人的台灣健保資料庫為一適合之研究族群.
4. 但影響藥物引起肝傷害的危險因子,如抽煙,肥胖,飲酒習慣…均沒紀錄在健保資料庫中,使用傳統用於罕見疾病的 case-control design 於找尋 matched control 時會有 bias.而使用 case-crossover design 時,control 就是 case 本身,避免了 control selection bias.故選擇使用.
5. 沒有論文曾使用 case-crossover design 來研究藥物引起肝傷害,故先進行方法學研究,與傳統 case-control design 對已知肝毒性的藥物進行結果分析,來判斷是否可用 case-crossover design 於藥物引起肝傷害之研究?
6. 利用 case-crossover design 來進行中藥與急性肝炎住院的相關研究.並比較在 B,C,酒精性肝炎及單純肝傷害住院不同族群的風險.
7. 利用 case-crossover design 來進行傳統肝毒性 NSAIDs 與 COX-2 selective inhibitors 造成急性肝傷害住院的相關比較研究.

# Chapter Ⅱ apply case-crossover design to assess the risk of DILI

## Objective

We applied case-control, and case-crossover designs to assess the estimated risks of liver injury related to well-known hepatoxic drugs, including isoniazid, rifampicin, erythromycin, and diclofenac.

## Material and methods

**National health insurance databases in Taiwan**

The dataset for the study was obtained from nationwide population-based databases obtained from the National Health Insurance (NHI), Taiwan. The NHI files are comprised of comprehensive information on all medications prescribed to all insured individuals. We conducted this study on both outpatient visits and admission databases from January 1, 1997 to December 31, 2004. There was an increasing insured population from 20,492,317 in 1997 to a total of 22,134,270 people in 2004. The cases included a group of hospitalized liver injury patients during the study period. Control subjects were selected from the 1,000,000 individual sub-sample which was randomly sampled from the total insured population. With strict confidentiality guidelines being closely followed in accordance with personal electronic data protection regulations, the Ethics Review Board at the National Taiwan University College of Public Health approved all confidentiality aspects of this study.

**Case selection**

Cases included hospitalized patients who were older than 18 years of age and who suffered from liver injuries. To prevent any case misclassification, we only included the incident cases with a primary diagnosis of liver injury, and we excluded cases with other diagnoses of admission or cases reported only from outpatient clinics. Primary diagnoses of liver injury coded by the International Classification of Diseases, 9th Revision (ICD-9) included acute and sub-acute necrosis of the liver (570), toxic hepatitis (573.3), other specified disorders of liver (573.8), and unspecified disorder of liver (573.9). Moreover, we excluded patients who had been diagnosed with the following conditions at any time before admission: viral hepatitis A, B, C, and other viral hepatitis (070.0 to 070.9) and carriers (V026.1 to V026.9), cytomegalovirus and coxsackie virus diseases and infectious mononucleosis (573.1 to 573.2), cholelithiasis (574.0 to 574.9), chronic liver disease, cirrhosis, alcoholic liver diseases, abscess of liver, portal pyemia, hepatic coma, portal hypertension, hepatorenal syndrome, chronic liver disease and chronic passive congestion of the liver (571.0 to 573.0), malignant neoplasm of liver and intrahepatic bile ducts (155.0 to 155.2), liver metastasis (197.7), carcinoma in situ of the liver and biliary system (230.8), and liver disorders during pregnancy (646.7).

**Target drugs and covariates**

We selected several well-known hepatoxic drugs that have been frequently used in the databases as our target drugs. This list included anti-tuberculosis drugs (isoniazid, rifampicin), antibiotics (erythromycin), and non-steroidal anti-inflammatory drugs (diclofenac). Other hepatoxic drugs and co-morbidity were considered as covariates in the models. We undertook a search of the Micromedex® database for a total of 702 generic drugs that had

been previously reported as having any connection with hepatotoxicity and the NHI in Taiwan regularly reimbursed 270 of them. We calculated the scores of Charlson Comorbidity Index by using ICD-9 codes to determine the condition of 1-year comorbidity.(43)

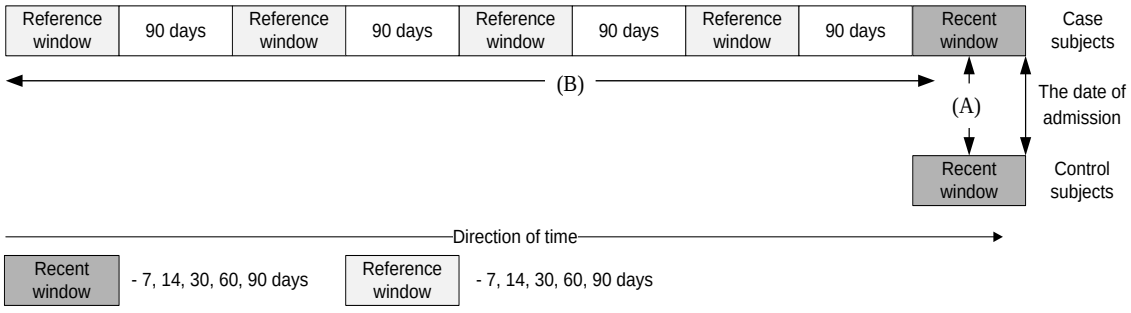
**Exposure windows**

An exposure window is an arbitrary unit of observation associated with the hypothesis being explored.(44) We applied the sensitivity analysis of 7, 14, 30, 60, and 90-day exposure windows according to the variable latent period between 5 and 90 days. (4) To prevent any carryover effect, we also set 90 days between recent or reference exposure windows in crossover designs.

**Selections of referents in the case-control and case-crossover designs**

First, we analyzed the datasets with a case-control design. Control subjects or referents were hospitalized patients over 18 years of age who had no previous diagnoses of liver injury nor any diseases or conditions in the exclusive criteria of the cases. Four controls for each case were randomly selected from the 1,000,000 person sub-sample by matching admission date, age and gender. Then, in the case-crossover design, we set four reference windows with the same duration before the recent window. (Figure 1)

Figure 1. Timeline of the recent and reference exposure windows by case-control design (A), and case-crossover design (B).



**Data analysis**

The use of target drugs by each case subject during the recent window was contrasted with the use of the same drugs for the same duration by the four matched control subjects. The odds ratio (OR) was calculated for the exposure-odds of case subjects and control subjects and denoted as a case-control estimate. In the case-crossover design, the prevalence of our target drugs during the single recent window was contrasted with the prevalence over four reference windows among the same case subject. We then analyzed and calculated the ORs of four hepatoxic drugs by the case-crossover design during the 7, 14, 30, 60, and 90-day exposure windows. In view of the fact that the designs of these studies were one case matched with four controls or one recent window matched with four reference windows, we analyzed the data through a conditional logistic regression model to explore the association between hospitalization and our target drugs. By adjusting two covariates in the case-control design (the scores of Charlson Comorbidity Index and the frequency of the time-variant hepatoxic drugs during each exposure window) and by adjusting the latter one in the case-crossover design, we obtained the adjusted ORs. The analysis of the data was performed and modeled to calculate odds ratios and 95% confidence intervals (CIs) through the use of SAS version 9.13 software.

Because of the concern for the possibility of confounding by indication, we carried out the following sets of sensitivity analyses to test the robustness of our findings from the case-crossover design. Initially, the co-prescription of isoniazid and rifampicin might have shown more hepatotoxicity. We stratified and compared the risk of this subgroup with the risk of two subgroups with only isoniazid and only rifampicin alone. According to the following prescription

patterns, we then stratified with these subgroups. If we defined 30-day recent and reference windows by the use of a case-crossover design, then not all subjects could be a 1 to 4 match in the case-crossover design for lack of the reference windows during the study period. The other condition was that the subjects might have used these drugs before admission and then stopped using after admission. Finally, the co-morbidities may affect DILI[4]. We stratified the total population into subgroups with following co-morbidities (ICD-9 code) before admission: diabetes mellitus (250), essential hypertension (401), obesity and hyperlipidemia (272 and 278, respectively), chronic kidney disease and renal failure (585 to 586), hyperthyroidism (242), fasting, malnutrition (260 to 263), neoplasms (140 to 239), and alcohol-related diseases (291, 303, and 357.5). Pregnancy (646.7, V72.40-2, V22.0-2) was also considered at a period of 300 days prior to admission.

# Main findings

The adjusted odds ratios of 4,413 hospitalized liver injury patients during the 30-day exposure window showed significant increases for hepatoxic drugs by the case-control and case-crossover designs. The risk trends were similar by the case-control and case-crossover designs. (Table 3) The risk also had the potential to change in the different exposure windows for each drug when using the sensitivity analysis to assess the probable time for the development of DILI. ( Figure 2) The risk of admission with liver injury related to hepatoxic drugs could be assessed by all designs based on automated databases. In addition to the case-control design, the study provides alternative methods for screening the potential hepatotoxicity of drugs. (Appendix 1)

Table 3. Number of Exposed Subjects in the 30-day Recent and Reference Windows and Adjusted Odds Ratio between Isoniazid, Rifampicin, Erythromycin, and Diclofenac With Hospitalizations for Liver Injury by Case-Control and Case-Crossover Designs, 1997-2004.

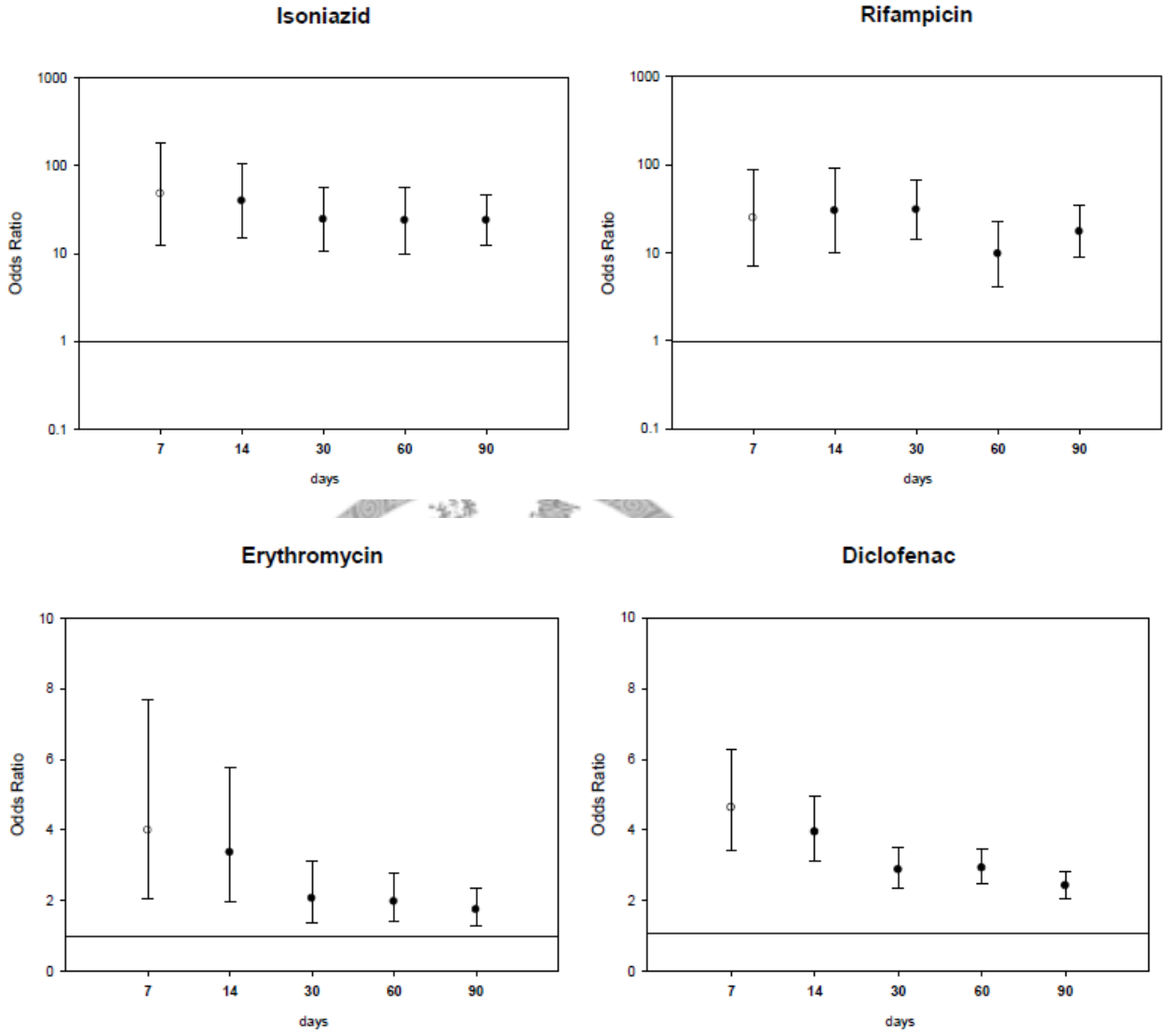
| | Exposed subjects during recent window | Exposed subjects during reference windows | Crude OR | 95% C.I. | Adjusted OR | 95% C.I. |
|---|---|---|---|---|---|---|
| **Isoniazid** | | | | | | |
| Case-control * | 100 | 13 | 35.91 | 19.27, 66.94 | 29.26 | 10.00, 85.64 |
| Case crossover † | 100 | 19 | 30.54 | 17.14, 54.42 | 24.35 | 10.69, 55.49 |
| **Rifampicin** | | | | | | |
| Case-control * | 105 | 17 | 27.66 | 16.10, 47.52 | 26.66 | 10.41, 68.28 |
| Case crossover † | 105 | 26 | 28.21 | 16.13, 49.33 | 30.75 | 14.08, 67.13 |
| **Erythromycin** | | | | | | |
| Case-control * | 75 | 124 | 2.45 | 1.83, 3.27 | 2.32 | 1.66, 3.25 |
| Case crossover † | 75 | 126 | 2.64 | 1.94, 3.59 | 2.06 | 1.35, 3.14 |
| **Diclofenac** | | | | | | |
| Case-control * | 383 | 489 | 3.35 | 2.92, 3.85 | 2.64 | 2.16, 3.24 |
| Case crossover † | 383 | 569 | 3.57 | 3.06, 4.16 | 2.87 | 2.35, 3.51 |

OR, odds ratio; CI, confidence interval.

* Adjusted for the frequency of these time-variant hepatoxic drugs during every exposure windows and the scores of Charlson co-morbidity score for one year before admission.

† Adjusted for the frequency of the time-variant hepatoxic drugs during every exposure windows.

Figure 2. Odds ratios between isoniazid, rifampicin, erythromycin, and diclofenac to admissions with liver injury during 7, 14, 30, 60, and 90-day exposure windows by a case-crossover design, 1997-2004



# Chapter Ⅲ risk of CHMs-induced liver injury

## Objective

Our study was conducted in an attempt to determine the association between the use of CHMs and the risk of hospitalizations related to acute hepatitis amongst the citizens of Taiwan.

## Material and methods

**Study subjects**

Out of the total population of 23 400 826 people enrolled within the NHI in Taiwan in 2002, such information was obtained on a random sample of 200 000 individuals. We selected this database throughout the study period of 1 January 1997 to 31 December 2002.

In order to prevent any misclassification of case diagnoses, we only used the major diagnosis of admission as the definition of cases instead of minor diagnoses of admission or any diagnoses from the outpatient clinics. In accordance with the major diagnosis for admission under the International Classification of Diseases, 9th Revision (ICD-9) code, the diagnoses for this study included acute viral hepatitis B (ICD-9 070.3, 070.31, 070.2, 070.21), acute viral hepatitis C (ICD-9 070.41, 070.51), acute and subacute necrosis of the liver, acute hepatic failure (ICD-9 570), unspecified hepatitis, drug-induced

hepatitis (ICD-9 573.3), and alcoholic hepatitis (ICD-9 571.1). We followed the criteria of drug-induced liver injury regarding chronological relationship and etiologic factors which could be found in our database to stratify and exclude.(4) We excluded cholelithiasis (ICD-9 574.0 to 574.9) and any rare codes where acute hepatitis was related to other etiological factors, such as pregnancy, congenital defects, and any other kinds of virus or bacteria.

The patients diagnosed at any time during their patient visits or hospitalizations as hepatitis B or C carriers were classified as viral hepatitis and further divided into hepatitis B or C. The other patients were classified as nonviral hepatitis and further divided into nonalcoholic hepatitis and alcoholic hepatitis. Nonviral, nonalcoholic hepatitis included acute and subacute necrosis of the liver, acute hepatic failure, unspecified hepatitis, and drug-induced hepatitis.

**Case-crossover design**

Since there are so many determinants, or potential confounders, for acute hepatitis, we felt that the standard case-control design may not work so effectively among subjects recruited from an administrative database; we therefore applied the case-crossover design, proposed by Maclure,(41) as a means of controlling for factors within the subjects. In such a way, any potential selection bias within the controls can be eliminated, since each case acts as its own control.

In drug-safety studies, the likelihood of prescribing a particular medication to a specific patient may well change over time. We have therefore adopted the symmetrical bidirectional crossover design, which uses the prior and posterior symmetrical periods as controls in order to avoid any potential bias relating to time trends. (39)

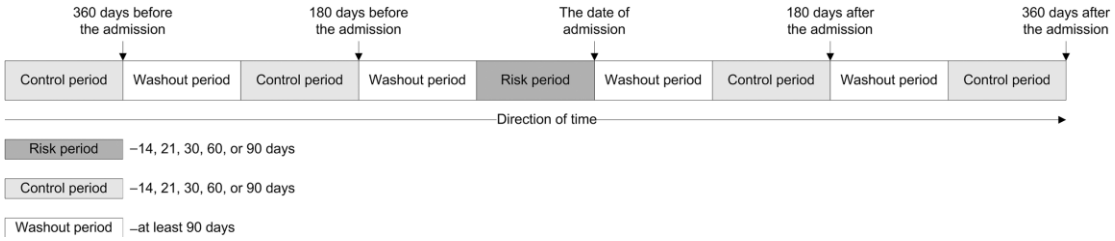
**Case and control exposure windows and washout periods**

The important consideration in this study was the length of the exposure time period. In order to make appropriate assumptions on the latent and induction times for possible CHM hepatotoxicity, we searched all of the available information on adverse effects from the CHM reports. Unfortunately, however, the range of latent time periods seemed rather wide, ranging between 1 week and 11 months.

Given that the latency period for the conventional drugs ranged between 5 days and 90 days,(4) we decided to use five exposure windows, set at 14, 21, 30, 60, and 90 days for the sensitivity analysis. In the same way, it was also necessary to allow for a washout period for each of the major prescriptions. Given that transaminase elevation in CHM-related hepatitis usually recovers within 8 days to 3 months, 90 days was selected as the washout period.

In this study, information was collected on prescriptions during the case (risk) periods prior to the hospitalizations events due to hepatitis. Two prior control periods were selected, with the exposure times before 180 days and 360 days prior to the date of admission. In the same way, two later control periods were selected before 180 days and 360 days after the date of admission (Figure 3).

**Figure 3** Timeline of the risk and four control periods.



After a comprehensive review of the related literature, we found that a number of herbs used in CHM were suspected as being hepatoxic; these include *Radix Scutellariae*, *Radix Bupleuri*, *Herba Ephedrae*, *Radix Polygoni Multiflori*, *Atractylodis macrocephalae rhizome*, *Radix Glycyrrhizae*, *Radix Paeoniae*, *Cortex Moutan*, and *Cortex Dictamni.*

We also undertook a review of the complete list of CHM products and revealed a total of 474 different prescriptions, each of which contained the aforementioned herbs, either as single elements or mixed formulae. An investigation was undertaken of the detailed records of hepatoxic CHM prescriptions during the risk periods. We then calculated the cumulative dose of every single herb within the formulae, based upon the concentrated mixed formulae which different CHM companies and estimated the crude dosage of the herbs in terms of both the weight and the concentrated proportions. The cumulative dosages of different hepatoxic conventional medicines were also calculated by adding together the total dosages prescribed during the risk periods.

**Covariates for adjustment**

In order to address the issue of potential bias from the simultaneous prescription of suspected hepatoxic CHMs and conventional drugs, we undertook a search of the Micromedex database for conventional drugs reported as having some connection with hepatotoxicity. Of the total of 702 generic drugs found (28 coprescriptions were excluded), 224 were regularly reimbursed by the NHI in Taiwan; these were therefore used as covariates for adjustment in the subsequent analysis.

**Statistical analysis**

Since the design of this study was aimed at enabling the analysis of one

case period matched with two prior, and two later, control periods, we applied matched conditional logistic regression to model the association between hospitalization and CHM prescriptions, whilst also controlling for potential confounding by other conventional medications. We then calculated the odds ratio and the 95% confidence intervals (CI) between the admission and the CHMs prescribed. The analysis of the data was performed using the SAS version 8.0 software (SAS Institute, Cary, NC, USA).

## Main findings

We have found that among the 200 000 individuals randomly selected from the NHI database during the 1997–2002 study period, there was about a 3.5-fold increase in the frequency of hospitalizations relating to acute nonviral, nonalcoholic hepatitis in CHM users. (Table 4) Our results provide additional safety information on the use of CHMs, with the finding that there is some increased risk of hospitalization relating to acute hepatitis among CHM users. (Appendix 3)

**Table 4** Crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) for acute hepatitis hospitalizations by the consumption of Chinese herbal medicines within 30- and 60-day risk periods

| Diseases | Exposed no. of cases | Exposed no. of controls | Crude OR | 95% CI | *P*-value | Adjusted OR[†] | 95% CI | *P*-value |
|---|---|---|---|---|---|---|---|---|
| 30-day risk period | | | | | | | | |
| Viral hepatitis | 22 | 55 | 2.0 | 1.1,3.6 | 0.03 | 1.4 | 0.7,2.8 | 0.35 |
| Hepatitis B | 17 | 40 | 2.3 | 1.1,4.7 | 0.03 | 1.2 | 0.5,2.9 | 0.62 |
| Hepatitis C | 2 | 12 | 0.6 | 0.1,3.0 | 0.59 | 0.6 | 0.1,3.2 | 0.60 |
| Hepatitis B and C | 3 | 3 | 7.8 | 0.8,78.8 | 0.08 | 8.8 | 0.8,98.1 | 0.07 |
| Nonviral hepatitis | 11 | 25 | 3.3 | 1.3,8.3 | 0.01 | 3.3 | 1.2,9.1 | 0.02 |
| Nonalcoholic Hepatitis | 12 | 24 | 3.3 | 1.2,8.5 | 0.01 | 3.4 | 1.1,9.8 | 0.03 |
| Alcoholic hepatitis | 1 | 1 | 4.0 | 0.3,64.0 | 0.33 | 2.9 | 0.2,48.3 | 0.46 |
| Total | 35 | 80 | 2.3 | 1.4,3.9 | <0.01 | 1.8 | 1.0,3.2 | 0.04 |
| 60-day risk period | | | | | | | | |
| Viral Hepatitis | 27 | 73 | 1.8 | 1.0,3.1 | 0.05 | 1.4 | 0.7,2.5 | 0.26 |
| Hepatitis B | 20 | 53 | 1.8 | 0.9,3.5 | 0.08 | 1.1 | 0.5,2.4 | 0.65 |
| Hepatitis C | 4 | 16 | 1.2 | 0.3,4.5 | 0.78 | 1.1 | 0.3,4.5 | 0.85 |
| Hepatitis B and C | 3 | 4 | 5.2 | 0.5,54.2 | 0.17 | 9.8 | 0.8, 126.5 | 0.08 |
| Nonviral hepatitis | 18 | 44 | 2.8 | 1.3,6.2 | 0.02 | 2.6 | 1.1,5.8 | 0.03 |
| Non-alcoholic Hepatitis | 14 | 38 | 2.6 | 1.1,6.5 | 0.03 | 2.4 | 1.0,6.0 | 0.06 |
| Alcoholic hepatitis | 4 | 6 | 3.6 | 0.7,17.6 | 0.43 | 3.4 | 0.5,23.5 | 0.26 |
| Total | 45 | 117 | 2.1 | 1.3,3.3 | <0.01 | 1.7 | 1.0,2.8 | 0.03 |

[†]Adjusted for prescriptions of conventional medicines with hepatotoxicity.

# Chapter Ⅳ risk of COX-2 inhibitors-induced liver injury

## Objective

Our study was conducted in an attempt to determine the association between the use of hepatoxic NSAIDs, COX-2 selective inhibitors and the risk of hospitalizations relating to acute hepatitis.

## Material and methods

**Data source**

The dataset was obtained from the NHI database in Taiwan. The NHI files consist of comprehensive information on all medications prescribed to all insured individuals. We utilized both the outpatient visits and admission databases, which included information on gender, date of birth, date of admission, date of discharge, dates of visits, admission diagnoses, outpatient visit diagnoses and prescription information (e.g., names, dosages, days, and expenditures). The Ethics Review Board at the National Taiwan University College of Public Health approved this study, with strict confidentiality guidelines being closely followed in accordance with personal electronic data protection regulations.

Study period and population

Three COX-2 selective inhibitors (rofecoxib, celecoxib and nimesulide) are

commercially available in Taiwan. The NHI began to reimburse for celecoxib, rofecoxib and nimesulide on April 1, 2001, July 1, 2001, and March 1, 2003, respectively, but rofecoxib was withdrawn from the market in October 2004 because of reports of cardiovascular events. For these reasons, we chose a study period that started on April 1, 2001 and ended on the last date in the database that we applied for, December 31, 2004. The number of people in the annual dataset for all publicly insured people ranged from 21,653,555 in 2001 to 22,134,270 in 2004.

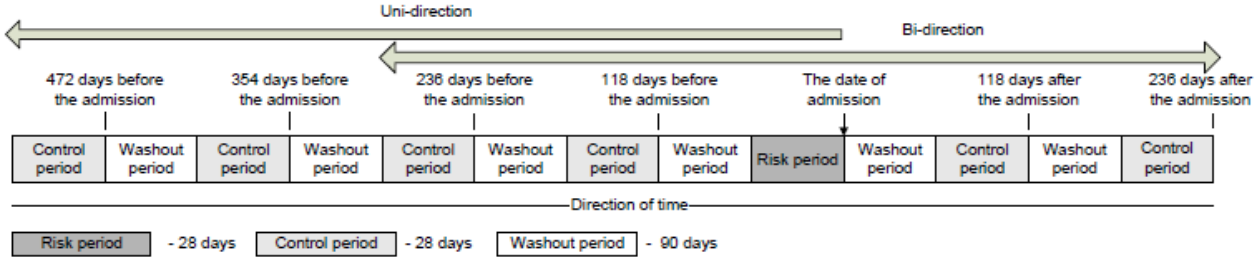
In order to prevent any misclassification of case diagnoses, we selected the study population from all publicly insured people by using the major diagnosis at admission as the definition of each case instead of minor diagnoses of admission or any diagnoses from outpatient clinics. The diagnoses in the NHI database generally follow the International Classification of Diseases, 9th Revision (ICD-9) codes. We included only the diagnoses of acute and sub-acute necrosis of the liver (ICD-9 570) and toxic (noninfectious) hepatitis (ICD-9 573.3). We excluded patients diagnosed before admission with viral hepatitis A, B, C or other viral hepatitis (ICD-9 070.0 to 070.9), viral hepatitis B or C carriers (ICD-9 V026.1 to V026.9), hepatitis in viral and other infectious diseases classified elsewhere (ICD-9 573.1 to 573.2), cholelithiasis (ICD-9 574.0 to 574.9), chronic liver disease and cirrhosis (ICD-9 571.0 to 571.9), liver abscess and sequelae of chronic liver disease (ICD-9 572.0 to 572.8), chronic passive congestion of liver (ICD-9 573.0), malignant neoplasm of liver and intrahepatic bile ducts (ICD-9 155.0 to 155.2), or liver metastasis (ICD-9 230.8). Because subjects might have been admitted more than once, we selected the earliest admission date for each individual.

**Case-crossover design**

Since there are many determinants, or potential confounders, of acute hepatitis, we applied the case-crossover design proposed by Maclure (41) as a means of controlling for factors within subjects. Thus, there was no control selection bias since each case acted as its own control. In drug safety studies, the likelihood of prescribing a new medication may change over time. (45) To avoid any potential bias related to time trends, we have therefore adopted uni- and symmetrically bi-directional case crossover designs, which use the four prior and two prior-posterior symmetrical periods as controls. (46) The important consideration in this design was the overall length of the exposure time period, based on case or population history. (44) To make appropriate assumptions on the latent and induction times, we searched all of the available information on adverse effects from the case reports of celecoxib, rofecoxib and nimesulide. Given that the latency period for conventional hepatoxic drugs ranges between 5 and 90 days (4) and any case occurring more than 15 day (for acute hepatocellular toxicity) or 30 days (for cholestasis) after drug withdrawal can be excluded, we decided to use 28 days as exposure windows to ensure that the treatment is not stopped more than 15 days before onset of hepatotoxicity. (47) Information was collected on prescriptions taken during each exposure window. In addition, given that transaminase elevation in case reports usually recovered within 14 days to 4 months, 90 days was selected as the washout period. For example, four prior control periods were selected, with exposure times beginning at 118, 236, 354 and 472 days prior to the date of admission. In the same way, two prior control and two later control periods were selected, beginning at 118 days and 236 days before and after the date of admission (Figure 4). In brief, there were two kinds of models to analyze by uni-directional and bi-directional case-crossover designs during the 28 days

periods. After comparing the results of the two models, we selected the model with the uni-directional case-crossover design for further sensitivity analysis.

Figure 4. Timeline of the risk and four uni- and bi-directional control periods




**Exposures of interest and covariates for adjustment**

Furthermore, we undertook a search of the Micromedex® database for drugs reported as having any connection with hepatotoxicity. A total of 702 generic drugs were found, and the NHI in Taiwan regularly reimbursed 270 of them. We grouped them by anatomical therapeutic chemical (ATC) code and used them for adjustment. For example, if the ATC codes were M01AB, M01AC, M01AE, M01AG, M01AX, M02AA, N02BA, and B01AC, we classified these 26 drugs as ‘hepatoxic NSAIDs’; J01 as 70 ‘antibacterial drugs’; J04A as 5 ‘anti-tuberculosis drugs’; N02CA, N03AA, N03AE, N05BA, and N05CD as 14 ‘benzodiazepine and barbiturate drugs’; and the residues as 155 ‘other hepatoxic drugs’. Also, there were reports of hepatotoxicity from using Chinese herbal medicines. (48, 49) Therefore, prescriptions of Chinese herbal medicines were grouped as ‘Chinese herbs’.

We selected the two most frequent traditional NSAIDs (diclofenac and ibuprofen), three COX-2 selective inhibitors (celecoxib, rofecoxib and nimesulide) and other hepatoxic NSAIDs (21 hepatoxic NSAIDs, excluding the previous five drugs) to compare the odds ratios between them.

However, in order to investigate the condition of celecoxib prescription during the studt period, we further observed the characteristics, prescribing frequencies and patterns of the cases that had celecoxib prescriptions in the

risk period and the number of prescriptions for celecoxib taken all subjects per year. To clarify the dose-response relationship between the COX-2 selective inhibitors and hospitalization, we compared the daily doses of prescriptions on the date closest to admission and cumulative doses during the risk period.

**Sensitivity analysis and external adjustment for unmeasured confounders**

Finally, we carried out three sets of sensitivity analyses to test the robustness of our findings. First, if we defined 28-day risk and control periods by using a case-crossover design as mentioned before, not all subjects could be included in a 1-to-4 match uni-directional case-crossover design for lack of control periods during the study period. In addition, some individuals had further records in our study databases after admission. Furthermore, some subjects might have used celecoxib but stopped after admission. According to these different prescribing patterns, we stratified the sample according to these subgroups. Second, sex, older age and the status of diseases may affect DILI. (8) Common approved indications for treatment with celecoxib and rofecoxib were osteoarthritis (ICD-9 715) and rheumatoid arthritis (ICD-9 714.0, 714.3). Then, we explored the data for any of the following conditions or co-morbidities before admission for acute non-viral hepatitis: diabetes mellitus (ICD-9 250), essential hypertension (ICD-9 401), obesity and hyperlipidemia (ICD-9 272, 278), chronic kidney disease and renal failure (ICD-9 585 to 586), hyperthyroidism (ICD-9 242), fasting and malnutrition (ICD-9 260 to 263), or neoplasms (ICD-9 140 to 239). Pregnancy (ICD-9 646.7, V72.40 to 72.42, V22.0 to 22.2) was also considered for 300 days before admission. We stratified the total population into subgroups according to the three co-morbidities that were diagnosed most frequently. Third, we grouped the

hepatoxic drugs into classes to adjust for the fact that some specific drugs within a class might be hepatoxic. We also stratified them into subgroups according to the seven most frequent co-prescriptions that were used by our subjects during the study period.

**Data analysis**

Since the design of this study utilized one case period matched with four control periods, we analyzed the data through construction of conditional logistic regression models to explore the association between hospitalization and prescriptions while controlling for antibiotics, anti-tuberculosis drugs, benzodiazepines and barbiturates, Chinese herbs and other hepatoxic drugs. We then calculated odds ratios and 95% confidence intervals (CIs). The analysis of the data was performed using SAS version 9.13 software (SAS Institute Inc., Cary, NC).

**Main findings**

Our study found that nimesulide, dicofenac, ibuprofen and other hepatoxic NSAIDs increased the risk of hospitalization for acute hepatitis, which corroborates previous studies. Moreover, there was a significantly higher risk in the use of celecoxib, which has never been reported before. Our results provide additional safety information for the use of celecoxib as well as hepatoxic NSAIDs, with the finding that there was an increased risk of hospitalization for acute hepatitis. Further mechanistic research is warranted for celecoxib's hepatotoxicity. (Appendix 2)

Table 5. Adjusted odds ratios of COX-2 selective inhibitors, diclofenac, ibuprofen and other hepatoxic NSAIDs on hospitalizations with acute non-viral hepatitis during the 28 days of the risk period with prior and posterior control periods, 2001-2004

| | | | Prior controls | | | | Prior and posterior controls | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Cases (N=4,519) | Controls (N=15,427) | OR[a] | 95% CI | | Controls (N=16,670) | OR[a] | 95% CI | |
| Celecoxib | | 35 | 63 | 1.92 | 1.38 | 2.69 | 73 | 1.71 | 1.23 | 2.39 |
| Daily dose[b] | ≥200 mg | 28 | 53 | 1.86 | 1.28 | 2.71 | 63 | 1.63 | 1.12 | 2.36 |
| | <200 mg | 7 | 10 | 2.20 | 1.04 | 4.64 | 10 | 2.17 | 1.03 | 4.58 |
| Cumulative | ≥2000 mg | 25 | 51 | 1.77 | 1.19 | 2.63 | 55 | 1.65 | 1.11 | 2.45 |
| dose[c] | <2000 mg | 10 | 12 | 2.45 | 1.31 | 4.58 | 18 | 1.89 | 1.01 | 3.52 |
| Rofecoxib | | 19 | 45 | 1.60 | 1.01 | 2.51 | 66 | 1.18 | 0.75 | 1.85 |
| Nimesulide | | 30 | 31 | 2.63 | 1.83 | 3.77 | 42 | 2.19 | 1.53 | 3.15 |
| Diclofenac | | 580 | 794 | 2.22 | 2.05 | 2.42 | 889 | 2.06 | 1.90 | 2.24 |
| Ibuprofen | | 287 | 318 | 2.51 | 2.23 | 2.82 | 383 | 2.24 | 1.99 | 2.52 |
| Other hepatoxic NSAIDs[d] | | 918 | 1,350 | 2.13 | 2.00 | 2.28 | 1,594 | 1.91 | 1.78 | 2.04 |

COX-2, cyclo-oxygenase-2; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; CI, confidence interval.

[a] Adjusted for antibacterial drugs, anti-tuberculosis drugs, benzodiazepines and barbiturates, Chinese herbs and other hepatoxic drugs.

[b] Daily doses of prescriptions on the date closest to admission.

[c]. Cumulative doses of prescriptions during the risk period.

[d]. Other hepatoxic NSAIDs: all hepatoxic NSAIDs except celecoxib, rofecoxib, nimesulide, diclofenac, and ibuprofen.

## Chapter Ⅴ conclusions

Our study is the first to apply case-crossover design in the detect risk of DILI in the automated database. Then we use this design to access and find the risks of CHMs and COX-2 selective inhibitors. And we found, there was about a 3.5-fold increase in the frequency of hospitalizations relating to acute nonviral, nonalcoholic hepatitis in CHM users. Moreover, we also found that a significantly higher risk hospitalizations relating to liver injury in the use of celecoxib.

We provided above safety informations to the CHM and celecoxib users. And we hope physicians could pay more attention to prescribe these medications and take biochemical test if suspecting DILI.

In the future, we will use case-crossover design to survey the risk of other potential hepatoxic medications to provide more safety information. Furthermore, the mechanistic research will be warranted for the hepatotoxicity about the CHMs and drugs.

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# Appendix

**1. Use of Hepatoxic Medications and the Risk of Liver Injury: An Observational Study Using Case-Control and Case-Crossover Designs (Manuscript)**
**Reviewed by *Epidemiology***

**Manuscript:**

Use of Hepatoxic Medications and the Risk of Liver Injury: An Observational Study Using Case-Control and Case-Crossover Designs

**Abstract**
Background: Relatively few epidemiological studies concerning drug-induced liver injuries have been conducted because of both the rarity and variant latent periods of the injuries. In this study, our observational study was conducted to assess if case-control and case-crossover designs could be applied to detect the risk of hepatoxic drugs on liver injury in the automated databases.
Methods: The study was conducted on approximately 22 million people enrolled in Taiwan's national health insurance database from January 1, 1997 to December 31, 2004. We applied case-control and case-crossover designs to assess the estimated risks of liver injury related to well-known hepatoxic drugs, including isoniazid, rifampicin, erythromycin, and diclofenac. Additionally, we also estimated the risks in different exposure windows by sensitivity analysis.
Results: The adjusted odds ratios of 4,413 hospitalized liver injury patients during the 30-day exposure window showed significant increases for hepatoxic drugs by the case-control and case-crossover designs. The adjusted odds ratios for the hepatoxic drugs during the 7-day exposure window were largest by the case-crossover design among the different windows.
Conclusions: The risk of admission with liver injury related to hepatoxic drugs could be assessed by all designs based on automated databases. In addition to the case-control design, the study provides alternative methods for screening the potential hepatotoxicity of drugs.

Background

Drug toxicities are the leading cause of liver failure in the United States.[1] In addition, liver damage is a major reason for withdrawal of a drug from the market. [2] However, relatively few epidemiological studies investigating drug-induced liver injury (DILI) have been published, even though the literature on the clinical, biologic, and pathologic features is extensive and reflects numerous case reports and experimental studies. [3] The prevalence of DILI ranges from 1 in 10,000 to 1 in 100,000 and widely varies when comparing one drug to another. Its rarity makes it impossible to be detected in clinical trials and also extremely difficult to be discovered through spontaneous reporting. [4] Thus, using an automated database with a large sample size is an ideal way for detecting DILI, especially when both exposure and the event are rare in the population.

Case-control design is a suitable choice for studying rare diseases, including adverse drug reaction. [5] However, there may be potential confounders that have not been recorded in the automated databases used for analysis. In 1991, Maclure proposed the case-crossover design, which can deal with this problem as a means of controlling for factors within subjects. [6] Therefore, our observational study was conducted to assess if these designs could be applied to detect the risk of hepatoxic drugs on liver injury. Moreover,

we estimated the risk in different exposure windows by sensitivity analysis, [7] because the latent period of DILI may vary widely among individuals. [4]

## Methods

### National health insurance databases in Taiwan

The dataset for the study was obtained from nationwide population-based databases obtained from the National Health Insurance (NHI), Taiwan. The NHI files are comprised of comprehensive information on all medications prescribed to all insured individuals. We conducted this study on both outpatient visits and admission databases from January 1, 1997 to December 31, 2004. There was an increasing insured population from 20,492,317 in 1997 to a total of 22,134,270 people in 2004. The cases included a group of hospitalized liver injury patients during the study period. Control subjects were selected from the 1,000,000 individual sub-sample which was randomly sampled from the total insured population. With strict confidentiality guidelines being closely followed in accordance with personal electronic data protection regulations, the Ethics Review Board at the National Taiwan University College of Public Health approved all confidentiality aspects of this study.

Case selection

Cases included hospitalized patients who were older than 18 years of age and who suffered from liver injuries. To prevent any case misclassification, we only included the incident cases with a primary diagnosis of liver injury, and we excluded cases with other diagnoses of admission or cases reported only from outpatient clinics. Primary diagnoses of liver injury coded by the International Classification of Diseases, 9th Revision (ICD-9) included acute and sub-acute necrosis of the liver (570), toxic hepatitis (573.3), other specified disorders of liver (573.8), and unspecified disorder of liver (573.9). Moreover, we excluded patients who had been diagnosed with the following conditions at any time before admission: viral hepatitis A, B, C, and other viral hepatitis (070.0 to 070.9) and carriers (V026.1 to V026.9), cytomegalovirus and coxsackie virus diseases and infectious mononucleosis (573.1 to 573.2), cholelithiasis (574.0 to 574.9), chronic liver disease, cirrhosis, alcoholic liver diseases, abscess of liver, portal pyemia, hepatic coma, portal hypertension, hepatorenal syndrome, chronic liver disease and chronic passive congestion of the liver (571.0 to 573.0), malignant neoplasm of liver and intrahepatic bile ducts (155.0 to 155.2), liver metastasis (197.7), carcinoma in situ of the liver and biliary system (230.8), and liver disorders during pregnancy (646.7).

Target drugs and covariates

We selected several well-known hepatoxic drugs that have been frequently used in the databases as our target drugs. This list included anti-tuberculosis drugs (isoniazid, rifampicin), antibiotics (erythromycin), and non-steroidal anti-inflammatory drugs (diclofenac). Other hepatoxic drugs and co-morbidity were considered as covariates in the models. We undertook a search of the Micromedex® database [8] for a total of 702 generic drugs that had been previously reported as having any connection with hepatotoxicity and the NHI in Taiwan regularly reimbursed 270 of them. We calculated the scores of Charlson Comorbidity Index by using ICD-9 codes to determine the condition of 1-year comorbidity.[9]

Exposure windows

An exposure window is an arbitrary unit of observation associated with the hypothesis being explored.[10] We applied the sensitivity analysis of 7, 14, 30, 60, and 90-day exposure windows according to the variable latent period between 5 and 90 days.[11] To prevent any carryover effect, we also set 90 days between recent or reference exposure windows in crossover designs.

Selections of referents in the case-control and case-crossover designs

First, we analyzed the datasets with a case-control design. Control subjects or referents were hospitalized patients over 18 years of age who had no previous diagnoses of liver injury nor any diseases or conditions in the exclusive criteria of the cases. Four controls for each case were randomly selected from the 1,000,000 person sub-sample by matching admission date, age and gender. Then, in the case-crossover design, we set four reference windows with the same duration before the recent window.

Data analysis

The use of target drugs by each case subject during the recent window was contrasted with the use of the same drugs for the same duration by the four matched control subjects. The odds ratio (OR) was calculated for the exposure-odds of case subjects and control subjects and denoted as a case-control estimate. In the case-crossover design, the prevalence of our target drugs during the single recent window was contrasted with the prevalence over four reference windows among the same case subject. We then analyzed and calculated the ORs of four hepatoxic drugs by the

case-crossover design during the 7, 14, 30, 60, and 90-day exposure windows. In view of the fact that the designs of these studies were one case matched with four controls or one recent window matched with four reference windows, we analyzed the data through a conditional logistic regression model to explore the association between hospitalization and our target drugs. By adjusting two covariates in the case-control design (the scores of Charlson Comorbidity Index and the frequency of the time-variant hepatoxic drugs during each exposure window) and by adjusting the latter one in the case-crossover design, we obtained the adjusted ORs. The analysis of the data was performed and modeled to calculate odds ratios and 95% confidence intervals (CIs) through the use of SAS version 9.13 software (SAS Institute Inc., Cary, NC).

Because of the concern for the possibility of confounding by indication, we carried out the following sets of sensitivity analyses to test the robustness of our findings from the case-crossover design. Initially, the co-prescription of isoniazid and rifampicin might have shown more hepatotoxicity. We stratified and compared the risk of this subgroup with the risk of two subgroups with only isoniazid and only rifampicin alone. According to the following prescription patterns, we then stratified with these subgroups. If we defined 30-day recent

and reference windows by the use of a case-crossover design, then not all subjects could be a 1 to 4 match in the case-crossover design for lack of the reference windows during the study period. The other condition was that the subjects might have used these drugs before admission and then stopped using after admission. Finally, the co-morbidities may affect DILI.[4] We stratified the total population into subgroups with following co-morbidities (ICD-9 code) before admission: diabetes mellitus (250), essential hypertension (401), obesity and hyperlipidemia (272 and 278, respectively), chronic kidney disease and renal failure (585 to 586), hyperthyroidism (242), fasting, malnutrition (260 to 263), neoplasms (140 to 239), and alcohol-related diseases (291, 303, and 357.5). Pregnancy (646.7, V72.40-2, V22.0-2) was also considered at a period of 300 days prior to admission.

Results

From the database of all insured individuals of Taiwan's NHI database between January 1, 1997 and December 31, 2004, there were a total of 4,413 cases with at least one 90-day reference window during the study period. These cases were all obtained after conforming to the inclusive and exclusive criteria. Of the total patients, 41.3% were older than 60 years of age and the

mean (SD) age was 52.6 (20.0) years. If we defined the 90-day exposure window using the crossover designs, then the total number of subjects that could be matched for 1-to-1, 1-to-2, 1-to-3 and 1-to-4 was 384, 358, 269 and 3,402, respectively, for lack of reference windows within the study period. We found the five most common co-morbid diseases before admission were essential hypertension (15.8%), neoplasms (10.9%), diabetes mellitus (10.6%), obesity and hyperlipidemia (6.8%), and chronic kidney disease and renal failure (5.6%). These findings are summarized in Table 1.

In Table 2, adjusted ORs during the 30-day window proved to be significant between isoniazid, rifampicin, erythromycin, diclofenac and admissions with liver injury by case-control and case-crossover designs. There was a similar risk trend of isoniazid, rifampicin, erythromycin, and diclofenac by case-control and case-crossover designs. Figure revealed that the adjusted ORs of our hepatoxic drugs during the 7-day exposure window were largest when examining the data with the case-crossover design.

## Discussion

We found that the risk trends of admissions with liver injury associated with our hepatoxic drugs based on automated databases during the 30-day

exposure window were similar by the case-control and case-crossover designs. The risk also had the potential to change in the different exposure windows for each drug when using the sensitivity analysis to assess the probable time for the development of DILI.

After using the case-control design when adjusting for age, gender and admission date, our estimates were more conservative when compared with the ORs of previous studies.[12,13] However, there are other factors, such as drinking habits and gene variation, that can influence DILI.[4] The presence of these factors may bias the risk assessment and distort the conclusions. Nonetheless, because there typically are additional confounders that are unmeasured in the automated dataset, using a case-control design to study DILI may make it difficult to select matched controls that are representative of the source population that ultimately gives rise to the cases. Thus, we chose a case-crossover design to largely eliminate any potential selection bias within the controls in the case-control design. This is achieved because each case acts as its own control, even including confounders by indication of chronic diseases.[14] In the statistical analyses, constant users and nonusers all contributed to the risk estimation in the case-control analyses, but not in their case-crossover analyses.[15] Moreover, we were able to explain the temporal

rule of causality of DILI by selecting the recent and prior reference windows.[11,15] Although the risks between the case-crossover and case-control designs were similar during the 30-day exposure window in our results, the former design was designed to answer, "Were you doing anything (taking hepatoxic drug) unusual just before the episode (liver injury)?" While the latter design was designed to detect, "Why me?" or, "What is different about me?". [16] The subjects in the case group may have had special genotypes that increased their susceptibility to DILI.[17] For these reasons, if an automated database was used for analysis, the case-crossover design might be more suitable for screening the inherent hepatotoxicity of drugs than the typical case-control design.

Our target drugs have different utility patterns, including the fact that the treatment duration of isoniazid and rifampicin is usually long-term (more than six months), while erythromycin is intermittent (weeks) and diclofenac is transient (days). We derived our conclusions based on the results of previous studies to determine the various latent periods of our drugs. Isoniazid-induced liver injury occurred mostly during the first three months.[18] Hospitalization with acute liver injury may occur after an approximate 10-day course of erythromycin and may develop after initiating diclofenac from 9 days to 21

months.[13, 19, 20] Because the time window of interest can be varied easily by a case-crossover design, we can deal with such various types of exposure and the potential latent period of DILI.[14] Otherwise, because of the potential delay of drug effects and the need to achieve maximum induction time, we set 90 days between the exposure windows to avoid carryover effect.[10] Thus, we could infer the actual duration of the risk by examining the change in magnitude of ORs under different assumptions about the exposure windows and obtain the best estimate of duration with minimal non-differential misclassification..[6, 7, 14] However, after adopting the above procedures in analysis, we found that changes of ORs for four hepatoxic drugs during various exposure windows were different. Figure shows that the 7-day exposure window had the highest risk associated with all hepatoxic drugs. Concerning the low exposure of isoniazid and rifampicin in the reference window, we defined the 30-day exposure window for further analysis. Furthermore, our preliminary analysis showed that the OR during the 30-day exposure window just before admission was the largest. That is, the prevalence of exposure to these hepatoxic drugs was the highest during the most recent duration before admission. This finding fit within the temporal relation of DILI.[11]

Finally, to further clarify the misclassifications and potential confounders,

we conducted the sensitivity analyses by stratification. In our study, the results revealed no significant changes in the ORs of the subgroups with different prescription conditions, matched patterns, and co-morbidities. Otherwise, we observed that the risk of isoniazid- rifampicin co-prescription is larger than the risk induced by each of the drugs individually (Appendix). Although it would be nicer to have more discordant pairs to corroborate our findings, we have validated the results of our target drugs by the above sensitivity analyses.[21]

There are two potential limitations in such a study. A first limitation was the case-selection bias, although control-selection bias may be eliminated by the case-crossover design.[6] We are still concerned that there is no special code for DILI in the ICD-9 code.[3, 5] Moreover, DILI is a disease that is difficult to conclusively diagnose, and we did not have any direct access to the original clinical data to verify the diagnosis of etiological agent. Thus, to prevent a potential bias by misdiagnosis, our study was limited to hospitalized cases that were more likely to have correct diagnoses. In addition, we excluded hepatobiliary diseases with other possible causes to minimize potential confounding.

A second potential limitation of our study was exposure misclassification, such as patient non-compliance and out-of-pocket drugs. In our design, we

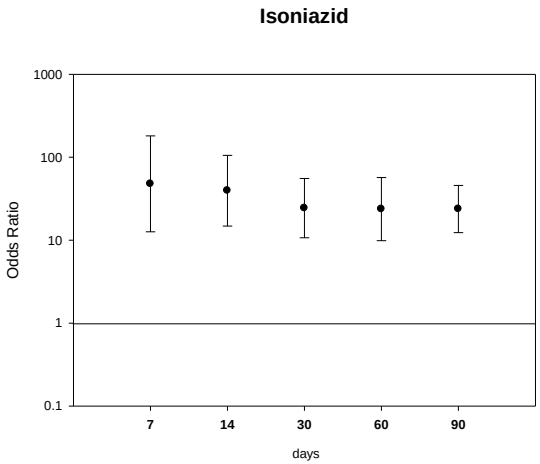
therefore applied a case-crossover design to partially control these unmeasured within-person confounders such as personal lifestyle factors. This type of limitation usually leads toward random misclassification and an under-estimation of risk.

The final limitation was the potential confounding by indication, a key problem in any observational study of drug safety. There are other characteristics of the prescribed drug, not the drug itself, to actually link between a drug and an adverse outcome.[22] These characteristics could not be examined in our automated database. However, we have adjusted the frequency of these time-variant hepatoxic drugs and the scores of co-morbidity in our study to at least partly control for this confounder. The indications of our target drugs, for the most part, did not appear to treat the symptoms of DILI, although the result could be slightly biased.

## Conclusion

Our study provides alternative methods, other than the conventional case-control design, to screen the hepatotoxicity of drugs. The incidence of drug-induced hepatotoxicity will increase when new drugs continually enter the

market.[23] This type of design would be helpful for the development of an epidemiologic study concerning DILI.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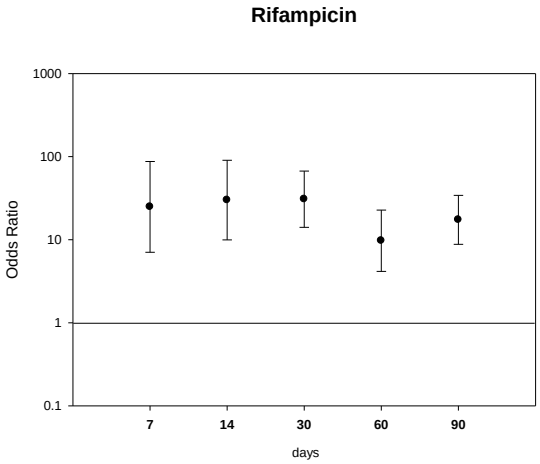
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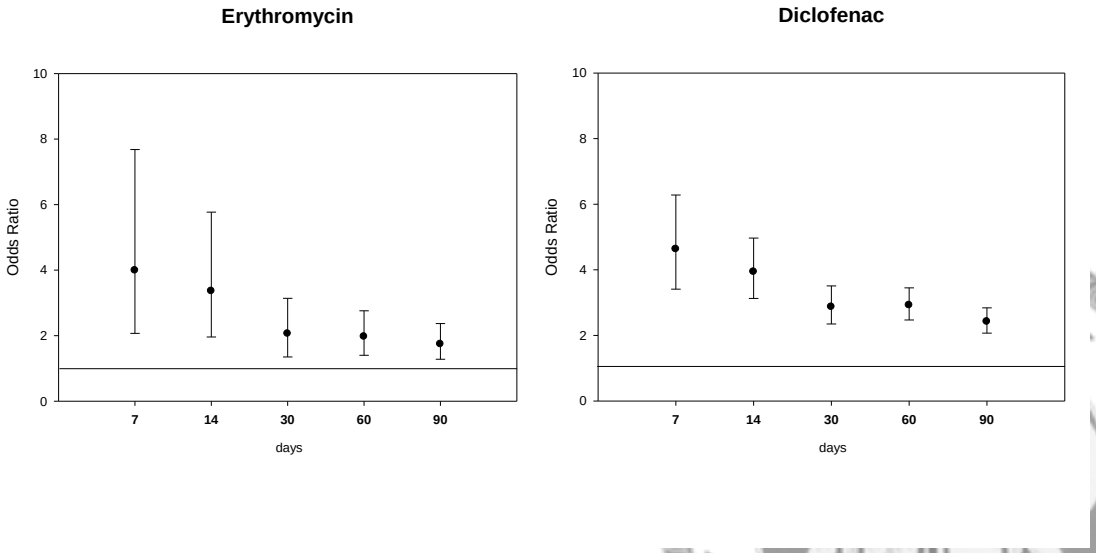


Figure. Odds ratios between isoniazid, rifampicin, erythromycin, and diclofenac to admissions with liver injury during 7, 14, 30, 60, and 90-day exposure windows by a case-crossover design, 1997-2004

Table 1. Characteristics, Co-morbidities, and Time-dependent Hepatoxic Drugs of Study Subjects Admitted With the Diagnosis of Acute Liver Injury, 1997-2004.

| Characteristics | Nos. | % |
|---|---|---|
| Total | 4,413 | 100.0 |
| Time independent covariates | | |
| Sex | | |
| Female | 1,860 | 42.1 |
| Male | 2,553 | 57.9 |
| Age (years) | | |
| 19-29 | 708 | 16.0 |
| 29-39 | 668 | 15.1 |
| 39-49 | 683 | 15.5 |
| 49-59 | 532 | 12.1 |
| ≥60 | 1,822 | 41.3 |
| Diagnosis (ICD-9 code) | | |
| Acute and sub-acute liver necrosis (570) | 2,229 | 50.5 |
| Toxic hepatitis (573.3) | 1,235 | 28.0 |
| Other specified liver disorders (573.8) | 784 | 17.8 |
| Unspecified liver disorder (573.9) | 165 | 3.7 |
| Scores of Charlson co-morbidity index before admission | | |
| 0 | 3,065 | 69.5 |

| | | |
|---|---|---|
| 1-2 | 858 | 19.4 |
| 3-5 | 410 | 9.3 |
| >5 | 80 | 1.8 |
| Co-morbidities may enhance susceptibility [a] | | |
| Essential hypertension | 696 | 15.8 |
| Neoplasms | 481 | 10.9 |
| Diabetes mellitus | 466 | 10.6 |
| Obesity and hyperlipidemia | 301 | 6.8 |
| Chronic kidney disease and renal failure | 246 | 5.6 |
| Fasting, malnutrition | 49 | 1.1 |
| Hyperthyroidism | 37 | 0.8 |
| Systemic lupus erythematosus | 33 | 0.7 |
| Alcohol-related diseases | 24 | 0.5 |
| Pregnancy | 10 | 0.2 |
| Time dependent covariates | | |
| Prescriptions before admission | Prescriptions | Per person |
| Hepatoxic medications | 186,234 | 42.2 |

Nos., Numbers; ICD-9, International Classification of Diseases, 9th Revision.

[a] Each subject might have none or more than one co-morbidity before admission.

Table 2. Number of Exposed Subjects in the 30-day Recent and Reference Windows and Adjusted Odds Ratio Between Isoniazid, Rifampicin, Erythromycin, and Diclofenac With Hospitalizations for Liver Injury by Case-Control and Case-Crossover Designs, 1997-2004.

| | Exposed subjects during recent window | Exposed subjects during reference windows | Crude OR | 95% C.I. | Adjusted OR | 95% C.I. |
|---|---|---|---|---|---|---|
| **Isoniazid** | | | | | | |
| Case-control [a] | 100 | 13 | 35.91 | 19.27, 66.94 | 29.26 | 10.00, 85.64 |
| Case crossover [b] | 100 | 19 | 30.54 | 17.14, 54.42 | 24.35 | 10.69, 55.49 |
| **Rifampicin** | | | | | | |
| Case-control [a] | 105 | 17 | 27.66 | 16.10, 47.52 | 26.66 | 10.41, 68.28 |
| Case crossover [b] | 105 | 26 | 28.21 | 16.13, 49.33 | 30.75 | 14.08, 67.13 |
| **Erythromycin** | | | | | | |
| Case-control [a] | 75 | 124 | 2.45 | 1.83, 3.27 | 2.32 | 1.66, 3.25 |
| Case crossover [b] | 75 | 126 | 2.64 | 1.94, 3.59 | 2.06 | 1.35, 3.14 |
| **Diclofenac** | | | | | | |
| Case-control [a] | 383 | 489 | 3.35 | 2.92, 3.85 | 2.64 | 2.16, 3.24 |
| Case crossover [b] | 383 | 569 | 3.57 | 3.06, 4.16 | 2.87 | 2.35, 3.51 |

OR, odds ratio; CI, confidence interval.

[a] Adjusted for the frequency of these time-variant hepatoxic drugs during every exposure windows and the scores of Charlson co-morbidity score for one year before admission.

[b] Adjusted for the frequency of the time-variant hepatoxic drugs during every exposure windows.

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Acknowledgments section:
Author Affiliations:
Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan (Chang-Hsing Lee, Jung-Der Wang, Pau-Chung Chen)
Department of Occupational Medicine, Ton Yen General Hospital, Hisnchu County, Taiwan (Chang-Hsing Lee)
Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan (Jung-Der Wang)
Department of Environmental and Occupational Medicine, National Taiwan University Hospital, Taipei, Taiwan (Jung-Der Wang)
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Appendix: Number of Exposed Subjects in the Recent and Reference Windows and Adjusted Odds Ratio Between Isoniazid, Rifampicin, Erythromycin, and Diclofenac for Hospitalizations With Liver Injury in the Sensitivity Analysis by a Case-Crossover Design, 1997-2004

| Models | Drugs | Exposed subjects during recent window | Exposed subjects during reference windows | Adjusted OR[a] | 95% C.I. |
|---|---|---|---|---|---|
| Co-prescriptions | Isoniazid+ rifampicin | 58 | 12 | 45.07 | 12.28, 165.37 |
| | Only isoniazid | 50 | 15 | 23.64 | 9.58, 58.32 |
| | Only rifampicin | 49 | 8 | 22.33 | 3.87, 128.94 |
| Matched patterns | | | | | |
| One recent to one reference windows | Isoniazid | 5 | 0 | - | - |
| | Rifampicin | 5 | 0 | - | - |
| | Erythromycin | 2 | 2 | 6.48 | 0.31, 135.34 |
| | Diclofenac | 14 | 9 | 5.32 | 1.40, 20.22 |
| One recent to two reference windows | Isoniazid | 4 | 0 | - | - |
| | Rifampicin | 4 | 0 | - | - |
| | Erythromycin | 0 | 3 | - | - |
| | Diclofenac | 23 | 10 | 8.30 | 2.22, 31.02 |
| One recent to three reference windows | Isoniazid | 4 | 1 | - | - |

| | | | | | |
|---|---|---|---|---|---|
| | Rifampicin | 2 | 0 | - | - |
| | Erythromycin | 7 | 3 | 9.16 | 0.78, 108.02 |
| | Diclofenac | 17 | 8 | 4.22 | 1.14, 15.56 |
| One recent to four reference windows | Isoniazid | 87 | 18 | 23.12 | 9.72, 55.00 |
| | Rifampicin | 94 | 26 | 26.67 | 12.13, 58.66 |
| | Erythromycin | 66 | 118 | 1.84 | 1.18, 2.86 |
| | Diclofenac | 329 | 542 | 2.64 | 2.14, 3.26 |
| Prescribing conditions | | | | | |
| Stop drugs after admission | Isoniazid | 52 | 16 | 13.70 | 5.55, 33.78 |
| | Rifampicin | 57 | 17 | 18.37 | 6.99, 48.26 |
| | Erythromycin | 46 | 72 | 2.24 | 1.31, 3.81 |
| | Diclofenac | 144 | 175 | 3.64 | 2.64, 5.03 |
| Co-morbidities | | | | | |
| Essential hypertension | Isoniazid | 2 | 2 | 9.30 | 0.66, 131.49 |
| | Rifampicin | 2 | 1 | - | - |
| | Erythromycin | 5 | 14 | 1.38 | 0.19, 9.91 |
| | Diclofenac | 32 | 57 | 4.08 | 2.00, 8.31 |
| Neoplasms | Isoniazid | 3 | 1 | - | - |
| | Rifampicin | 4 | 1 | - | - |
| | Erythromycin | 6 | 5 | 3.15 | 0.52, 19.18 |
| | Diclofenac | 19 | 41 | 1.94 | 0.84, 4.47 |
| Diabetes mellitus | Isoniazid | 3 | 0 | - | - |
| | Rifampicin | 3 | 0 | - | - |
| | Erythromycin | 5 | 11 | 1.39 | 0.24, 8.06 |
| | Diclofenac | 27 | 52 | 2.35 | 1.00, 5.51 |

OR, odds ratio; CI, confidence interval.

[a] Adjusted for the frequency of the time-variant hepatoxic drugs during every exposure windows.

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HEPATOLOGY

# Case-crossover study of hospitalization for acute hepatitis in Chinese herb users

Chang-Hsing Lee,*,† Jung-Der Wang*,‡,§ and Pau-Chung Chen*

*Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, and †Department of Occupational Medicine, Ton Yen General Hospital, Hisn-Chu County, and ‡Department of Internal Medicine and §Department of Environmental and Occupational Medicine, National Taiwan University Hospital, Taipei, Taiwan

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acute hepatitis, case-crossover studies, Chinese herbal drugs.

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**Correspondence**
Professor Pau-Chung Chen, Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, 17 Syujhou Road, Taipei 10055, Taiwan. Email: pchen@ntu.edu.tw

## Abstract

**Background and Aim:** Despite the increase in popularity of herbal products, there is growing concern over potential health hazards caused by the Chinese herbal medicines (CHMs) that are regularly reimbursed under the National Health Insurance system in Taiwan. This study attempts to determine the association between CHM prescriptions and acute hepatitis–related hospitalizations.

**Methods:** A case-crossover study was designed on 200 000 randomly selected individuals from the National Health Insurance Research Database who were then followed from 1997 to 2002. All medications taken in the 30- and 60-day periods prior to hospitalization were explored and compared with four control periods (the 180- and 360-day periods prior to and after the hospitalization). A conditional logistic regression model was then constructed to determine the odds of CHM being prescribed during these risk periods.

**Results:** There were a total of 12 cases with nonviral, nonalcoholic hepatitis patients who took CHM prescriptions during the 30-day risk or control periods. After adjustment for conventional hepatotoxic drugs, the odds ratio during the 30-day risk period was 3.4 (95% confidence interval [CI]: 1.1, 9.8) for nonviral, nonalcoholic acute hepatitis. A detailed historical review of CHMs for each patient revealed that the odds ratio increased to 4.2 for those prescribed formulae containing *Radix Paeoniae* (95% CI: 1.1, 15.7) and *Radix Glycyrrhizae* (95% CI: 1.2, 15.2).

**Conclusions:** Chinese herbal users revealed a slightly increased risk of acute hepatitis. We therefore recommend pharmacovigilance and active surveillance for CHMs suspected with hepatotoxicity.

## Introduction

Chinese herbal remedies (CHMs) have been used extensively as a means of treating various illnesses, among communities in China, Japan, Korea and Taiwan, for thousands of years. Since most of these medications are derived from herbs, there is often a perception among the regular users of these remedies that they are gentle and nontoxic;[1,2] and indeed, there has been a reported increase in the overall consumption of herbs or herbal medicines, over the past two decades. The use of herbal medicine in the United States has risen from 2.5% in 1990 to 12.1% in 1997[3] and 9.6% in 1999.[4]

Nevertheless, the Poison and Drug Center data collection program in Taiwan has recorded over 100 cases of poisoning following the consumption of herbs by individuals.[5] In addition to the infamous nephrotoxic events of herbs with aristolochic acid, an increasing number of herbal remedies are now being reported as hepatotoxic,[6] with such reports on CHMs including a variety of groups, such as *Radix Scutellariae*, *Radix Bupleuri*,[7] *Herba Ephedrae*,[8] *Radix Polygoni Multiflori,*[9] *Atractylodis macrocephalae rhizoma*, *Radix Glycyrrhizae*,[10] *Radix Paeoniae*, *Cortex Moutan*, and *Cortex Dictamni.*[11]

Most of these reports of poisonings were case reports, and not epidemiological studies; and indeed there have been relatively few epidemiological studies which have addressed the relationship between CHMs and worldwide hepatic adverse effects. Therefore, many cases of herbal-related toxic hepatitis may continue to go unrecognized and unreported.[12]

The National Health Insurance (NHI) program in Taiwan is a universal system of compulsory health insurance, which was implemented on 1 March 1995 and which has been providing coverage for 96.2% of the population of Taiwan since the end of 2000. For all medical care institutions contracted under the NHI system, the Taiwanese government reimburses not only general healthcare expenditure, but also the costs of prescriptions for CHMs. Since all of these claims for reimbursement must be submitted in computerized form, the availability of such data reveals that outpatient CHM accounts for 9% of all medications consumed in terms of frequency of use. These figures clearly indicate the

important role played by CHM in the Taiwanese healthcare system, with the CHM prescriptions covered by the NHI including virtually all of the popular CHMs (amounting to 780 different kinds of single herbs and mixed formulae) in concentrated extract form.[13] This computerized database of CHMs provides us with an invaluable opportunity to undertake a population-based study.

A study undertaken in the US found that 39% of liver disease patients had used some form of complementary/alternative medicine (CAM) prior to their diagnosis, and that the CAM used by 21% of these patients was some form of herbal medication, thereby raising concerns of potential hepatotoxicity.[14] The prevalence rates of viral hepatitis are very high in Taiwan; more than 90% of the general population having contacted hepatitis B virus (HBV) infection; and the prevalence of chronic infections is as high as 15–20%. Furthermore, the seroprevalence of the hepatitis C virus (HCV) amongst the general population has also been reported at 2–3%.[15]

The present study is therefore conducted in an attempt to determine the association between the use of CHMs and the risk of hospitalizations related to acute hepatitis amongst the citizens of Taiwan.

## Methods

### Data sources

The sampling cohort dataset was obtained from the NHI research database in Taiwan. The NHI sample files, compiled and managed by the National Health Research Institutes, comprise comprehensive information on all medications prescribed to individuals in Taiwan. Out of the total population of 23 400 826 people enrolled within the NHI in Taiwan in 2002, such information was obtained on a random sample of 200 000 individuals. We selected this database throughout the study period of 1 January 1997 to 31 December 2002.

We utilized both the outpatient visits and admission databases on the sample cohort, which included information on gender, date of birth, date of admission, date of discharge, dates of visits, admission diagnosis, outpatient visit diagnosis and prescription name, dosage, days, and expenditure. This study was approved by the ethics review board at the National Taiwan University College of Public Health, with strict confidentiality guidelines being closely followed in accordance with the personal electronic data protection regulations.

### Study subjects

In order to prevent any misclassification of case diagnoses, we only used the major diagnosis of admission as the definition of cases instead of minor diagnoses of admission or any diagnoses from the outpatient clinics. In accordance with the major diagnosis for admission under the International Classification of Diseases, 9th Revision (ICD-9) code, the diagnoses for this study included acute viral hepatitis B (ICD-9 070.3, 070.31, 070.2, 070.21), acute viral hepatitis C (ICD-9 070.41, 070.51), acute and subacute necrosis of the liver, acute hepatic failure (ICD-9 570), unspecified hepatitis, drug-induced hepatitis (ICD-9 573.3), and alcoholic hepatitis (ICD-9 571.1). We followed the criteria of drug-induced liver injury regarding chronological relationship and etiologic factors which could be found in our database to stratify and exclude.[16] We excluded cholelithiasis (ICD-9 574.0 to 574.9) and any rare codes where acute hepatitis was related to other etiological factors, such as pregnancy, congenital defects, and any other kinds of virus or bacteria.

The patients diagnosed at any time during their patient visits or hospitalizations as hepatitis B or C carriers were classified as viral hepatitis and further divided into hepatitis B or C. The other patients were classified as nonviral hepatitis and further divided into nonalcoholic hepatitis and alcoholic hepatitis. Nonviral, nonalcoholic hepatitis included acute and subacute necrosis of the liver, acute hepatic failure, unspecified hepatitis, and drug-induced hepatitis.

### Case-crossover design

Since there are so many determinants, or potential confounders, for acute hepatitis, we felt that the standard case-control design may not work so effectively among subjects recruited from an administrative database; we therefore applied the case-crossover design, proposed by Maclure,[17] as a means of controlling for factors within the subjects. In such a way, any potential selection bias within the controls can be eliminated, since each case acts as its own control.

In drug safety studies, the likelihood of prescribing a particular medication to a specific patient may well change over time. We have therefore adopted the symmetrical bidirectional crossover design, which uses the prior and posterior symmetrical periods as controls in order to avoid any potential bias relating to time trends.[18]

### Case and control exposure windows and washout periods

The important consideration in this study was the length of the exposure time period.[19] In order to make appropriate assumptions on the latent and induction times for possible CHM hepatotoxicity, we searched all of the available information on adverse effects from the CHM reports. Unfortunately, however, the range of latent time periods seemed rather wide, ranging between 1 week and 11 months.

Given that the latency period for the conventional drugs ranged between 5 days and 90 days,[16] we decided to use five exposure windows, set at 14, 21, 30, 60, and 90 days for the sensitivity analysis. In the same way, it was also necessary to allow for a washout period for each of the major prescriptions. Given that transaminase elevation in CHM-related hepatitis usually recovers within 8 days to 3 months, 90 days was selected as the washout period.

In this study, information was collected on prescriptions during the case (risk) periods prior to the hospitalizations events due to hepatitis. Two prior control periods were selected, with the exposure times before 180 days and 360 days prior to the date of admission. In the same way, two later control periods were selected before 180 days and 360 days after the date of admission (Fig. 1).


**Figure 1** Timeline of the risk and four control periods.

After a comprehensive review of the related literature, we found that a number of herbs used in CHM were suspected as being hepatotoxic; these include *Radix Scutellariae*, *Radix Bupleuri*,[7] *Herba Ephedrae*,[8] *Radix Polygoni Multiflori*,[9] *Atractylodis macrocephalae rhizome*, *Radix Glycyrrhizae*,[10] *Radix Paeoniae*, *Cortex Moutan*, and *Cortex Dictamni*.[11]

We also undertook a review of the complete list of CHM products and revealed a total of 474 different prescriptions, each of which contained the aforementioned herbs, either as single elements or mixed formulae. An investigation was undertaken of the detailed records of hepatotoxic CHM prescriptions during the risk periods. We then calculated the cumulative dose of every single herb within the formulae, based upon the concentrated mixed formulae which different CHM companies and estimated the crude dosage of the herbs in terms of both the weight and the concentrated proportions. The cumulative dosages of different hepatotoxic conventional medicines were also calculated by adding together the total dosages prescribed during the risk periods.

### Covariates for adjustment

In order to address the issue of potential bias from the simultaneous prescription of suspected hepatotoxic CHMs and conventional drugs, we undertook a search of the Micromedex database for conventional drugs reported as having some connection with hepatotoxicity.[20] Of the total of 702 generic drugs found (28 coprescriptions were excluded), 224 were regularly reimbursed by the NHI in Taiwan; these were therefore used as covariates for adjustment in the subsequent analysis.

### Statistical analysis

Since the design of this study was aimed at enabling the analysis of one case period matched with two prior, and two later, control periods, we applied matched conditional logistic regression to model the association between hospitalization and CHM prescriptions, whilst also controlling for potential confounding by other conventional medications. We then calculated the odds ratio and the 95% confidence intervals (CI) between the admission and the CHMs prescribed. The analysis of the data was performed using the SAS version 8.0 software (SAS Institute, Cary, NC, USA).

## Results

From the database of 200 000 individuals randomly sampled from the NHI database between 1997 and 2002, there were a total of 385 subjects conforming to the inclusion criteria. Among them, 14 subjects diagnosed as unclassified viral hepatitis were excluded from the study. In addition, 17 cases whose admission dates were before the end of March 1997 were also excluded in order to allow for the 90-day risk period. After we excluded these subjects, we found a total of 45 cases were 1-to-3 matched, and a further 40 cases were 1-to-2 matched, before subsequently performing conditional logistic regressions because of the duration of the database, which covered the period 1997–2002. Finally, 354 cases of hospitalization relating to acute hepatitis were obtained. The mean age was 45 ± 17.2, with 82.8% of the study sample falling within the range of 15–64 years of age. And they were divided into five groups as Table 1.

**Table 1** Characteristics of study subjects with initial admission diagnosis of acute hepatitis, 1997–2002†

| Characteristics | Total no. |
|---|---|
| Gender | |
| Male | 243 |
| Female | 111 |
| Age | |
| <15 years | 5 |
| 15–64 years | 293 |
| ≥65 years | 56 |
| Diseases | |
| Viral hepatitis | 197 |
| Hepatitis B | 137 |
| Hepatitis C | 50 |
| Hepatitis B & C | 10 |
| Nonviral hepatitis | 157 |
| Nonalcoholic hepatitis‡ | 126 |
| Alcoholic hepatitis | 31 |
| Total | 354 |

†Sample comprised of 200 000 randomly selected individuals from the National Health Insurance research database in Taiwan. ‡Includes acute and subacute necrosis of the liver, acute hepatic failure, unspecified hepatitis, and drug-induced hepatitis.

There were only 35 and 45 subjects who had received such prescriptions within the 30- and 60-day period. After calculating the odds ratios for the five different exposure periods selected for this study, we found that the odds ratio for 30 days was the largest and most significant; therefore, the 30-day period seemed the most probable time to the event. Among the 126 cases with nonviral, nonalcoholic hepatitis, only 12 cases who took CHM prescriptions during the 30-day risk periods showed a significant adjusted odds ratio of 3.4 (95% CI: 1.1, 9.8) (Table 2). Further examination of specific types of CHM prescriptions in nonviral, nonalcoholic hepatitis showed that products containing *Radix Paeoniae* and *Radix Glycyrrhizae* were probably involved (Table 3).

## Discussion

We have found that among the 200 000 individuals randomly selected from the NHI database during the 1997–2002 study

**Table 2** Crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) for acute hepatitis hospitalizations by the consumption of Chinese herbal medicines within 30- and 60-day risk periods

| Diseases | Exposed no. of cases | Exposed no. of controls | Crude OR | 95% CI | *P*-value | Adjusted OR† | 95% CI | *P*-value |
|---|---|---|---|---|---|---|---|---|
| 30-day risk period | | | | | | | | |
| Viral hepatitis | 22 | 55 | 2.0 | 1.1,3.6 | 0.03 | 1.4 | 0.7,2.8 | 0.35 |
| Hepatitis B | 17 | 40 | 2.3 | 1.1,4.7 | 0.03 | 1.2 | 0.5,2.9 | 0.62 |
| Hepatitis C | 2 | 12 | 0.6 | 0.1,3.0 | 0.59 | 0.6 | 0.1,3.2 | 0.60 |
| Hepatitis B and C | 3 | 3 | 7.8 | 0.8,78.8 | 0.08 | 8.8 | 0.8,98.1 | 0.07 |
| Nonviral hepatitis | 11 | 25 | 3.3 | 1.3,8.3 | 0.01 | 3.3 | 1.2,9.1 | 0.02 |
| Nonalcoholic Hepatitis | 12 | 24 | 3.3 | 1.2,8.5 | 0.01 | 3.4 | 1.1,9.8 | 0.03 |
| Alcoholic hepatitis | 1 | 1 | 4.0 | 0.3,64.0 | 0.33 | 2.9 | 0.2,48.3 | 0.46 |
| Total | 35 | 80 | 2.3 | 1.4,3.9 | <0.01 | 1.8 | 1.0,3.2 | 0.04 |
| 60-day risk period | | | | | | | | |
| Viral Hepatitis | 27 | 73 | 1.8 | 1.0,3.1 | 0.05 | 1.4 | 0.7,2.5 | 0.26 |
| Hepatitis B | 20 | 53 | 1.8 | 0.9,3.5 | 0.08 | 1.1 | 0.5,2.4 | 0.65 |
| Hepatitis C | 4 | 16 | 1.2 | 0.3,4.5 | 0.78 | 1.1 | 0.3,4.5 | 0.85 |
| Hepatitis B and C | 3 | 4 | 5.2 | 0.5,54.2 | 0.17 | 9.8 | 0.8, 126.5 | 0.08 |
| Nonviral hepatitis | 18 | 44 | 2.8 | 1.3,6.2 | 0.02 | 2.6 | 1.1,5.8 | 0.03 |
| Non-alcoholic Hepatitis | 14 | 38 | 2.6 | 1.1,6.5 | 0.03 | 2.4 | 1.0,6.0 | 0.06 |
| Alcoholic hepatitis | 4 | 6 | 3.6 | 0.7,17.6 | 0.43 | 3.4 | 0.5,23.5 | 0.26 |
| Total | 45 | 117 | 2.1 | 1.3,3.3 | <0.01 | 1.7 | 1.0,2.8 | 0.03 |

†Adjusted for prescriptions of conventional medicines with hepatotoxicity.

period, there was about a 3.5-fold increase in the frequency of hospitalizations relating to acute nonviral, nonalcoholic hepatitis in CHM users.

Given that we applied a case-crossover design to control for personal constitution and lifestyle factors, including the consumption of any regular over-the-counter medications, and given that we have also adjusted for all known conventional hepatotoxic drugs, there is low possibility of these factors explaining the increased risk. However, other alternative hypotheses such as drug interactions, altered metabolism due to genetic variability, taking a nonprescribed medication etc., might still be uncontrolled confounders.

There is, of course, always some concern with regard to the possibility that our cases may have been more severe, which would therefore lead to increased consumption of various forms of medication, including CHMs; however, since the respective periods of hospitalization for our cases and for viral hepatitis were not statistically different, that is $7.1 \pm 7$ vis-à-vis $7.4 \pm 5.7$ days, the likelihood of such potential confounding would appear low.

Although we tentatively conclude that the consumption of CHMs may lead to an increased risk of hospitalization with acute hepatitis, we admit that this study collected only 12 cases of hospitalization for nonviral and nonalcoholic hepatitis; therefore, future verification with a larger sample would seem to be necessary.

Furthermore, since HBV and HCV are hyperendemic in Taiwan,[15] the use of CHMs as an alternative method of management for patients with chronic viral hepatitis is common. In those patients with chronic HBV or HCV infections, there has also been a report of a higher prevalence of liver injury amongst users of herbal products.[21] After we have deliberately stratified these to obtain a more homogeneous comparison within each stratum, viral agents also fail to explain the increased risk. Amongst those subjects with hepatitis B, the crude odds ratio of hospitalization showed an increase of 2.3 where such patients had been prescribed CHMs; after adjustment with hepatotoxic conventional medications this became statistically nonsignificant (Table 2). This would therefore suggest that healthcare professionals in Taiwan must be more careful in their use of conventional medicines than CHMs among viral hepatitis carriers.

## Thirty-day risk periods

In this study, we have found 30 days to be the highest risk period with regard to the consumption of CHM prescriptions; however, the time window must of course be individualized to accommodate both for the hypothesized hazard period relating to the drug and the induction period after which the development of the outcome is presumed. Given that this study has explored the acute hepatotoxic effect, which usually lasts for about 2 to 3 weeks,[22,23] it differs significantly from the cumulative effects of chronic medications, which may require a substantially longer period of time; that is, 3 months or even longer.[24]

## Prescription time trend bias

In drug safety studies, the probability of a certain drug being prescribed to a specific patient may change over time, especially with new drugs being regularly introduced into the market.[25] However, from 1997 to 2002, the total frequency of CHM prescriptions increased slightly from 27 946 to $28\,912*10^3$ per year and there were no new mixtures of traditional Chinese medicinal products introduced into the NHI; thus any potential prescription time trend bias would have to be regarded as negligible in this study.

**Table 3** Crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) for acute hepatitis hospitalization by the consumption of suspected hepatotoxic Chinese herbal products within the 30-day risk period

| Chinese herbal medicine mixed formulae groups† | Exposed no. of cases/ controls | Viral hepatitis B | | | | | | Exposed no. of cases/ controls | Nonviral, nonalcoholic hepatitis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Crude OR | 95% CI | *P*-value | Adjusted OR‡ | 95% CI | *P*-value | | Crude OR | 95% CI | *P*-value | Adjusted OR‡ | 95% CI | *P*-value |
| *Radix Scutellariae* | 5/24 | 0.8 | 0.3, 2.4 | 0.73 | 0.6 | 0.2, 2.0 | 0.42 | 4/5 | 4.1 | 0. 9, 19.0 | 0.07 | 3.9 | 0.7, 20.8 | 0.10 |
| *Radix Paeoniae* | 8/29 | 1.2 | 0.4, 3.1 | 0.38 | 0.9 | 0.3, 3.0 | 0.62 | 8/12 | 5.3 | 1.5, 18.7 | 0.01 | 4.2 | 1.1, 15.7 | 0.03 |
| *Radix Glycyrrhizae* | 13/43 | 1.6 | 0.7, 3.5 | 0.42 | 0.9 | 0.3, 2.4 | 0.60 | 10/17 | 5.1 | 1.5, 17.4 | <0.01 | 4.2 | 1.2, 15.2 | 0.03 |
| *Radix Paeoniae* and *Radix Glycyrrhizae* | 9/26 | 1.6 | 0.6, 3.9 | 0.28 | 1.3 | 0.5, 3.9 | 0.48 | 8/11 | 5.5 | 1.6, 19.3 | <0.01 | 4.2 | 1.1, 15.8 | 0.03 |
| *Radix Scutellariae* and *Radix Glycyrrhizae* | 3/19 | 0.5 | 0.1, 2.2 | 0.38 | 0.5 | 0.1, 2.4 | 0.39 | 4/5 | 4.1 | 0.9, 19.0 | 0.07 | 3.9 | 0.7, 20.8 | 0.11 |
| *Radix Scutellariae* and *Radix Paeoniae* | 0/5 | – | – | – | – | – | – | 3/3 | 7.8 | 0.8, 78.8 | 0.08 | 7.3 | 0.7, 71.9 | 0.09 |
| *Rhizoma Atracylodis Macrocephalac* | 6/11 | 2.8 | 0.9, 9.3 | 0.06 | 1.1 | 0.3, 4.3 | 0.72 | 2/6 | 1.5 | 0.2, 10.0 | 0.68 | 1.3 | 0.2, 9.8 | 0.78 |
| *Cortex Moutan* | 3/5 | 2.3 | 0.5, 10.5 | 0.30 | 1.9 | 0.3, 14.3 | 0.51 | 1/1 | 3.5 | 0.2, 55.8 | 0.38 | 1.0 | 0.1, 19.9 | 0.98 |
| *Radix Bupleuri* | 7/12 | 4.3 | 1.2, 16.0 | 0.03 | 2.8 | 0.6, 12.3 | 0.18 | 4/11 | 1.7 | 0.4, 6.6 | 0.46 | 2.1 | 0.5, 9.3 | 0.30 |
| *Herba Ephedrae* | 2/8 | 1.0 | 0.2, 5.1 | 1.00 | 0.5 | 0.1, 3.2 | 0.45 | 2/1 | 8.0 | 0.7, 88.2 | 0.09 | 4.5 | 0.4, 49.6 | 0.22 |

†The formulae groups of Chinese herbal medicine prescriptions containing *Radix Polygoni Multiflori* and *Cortex Dictamni* were not used in the case and control periods. ‡Adjusted for prescriptions of conventional medicines with hepatotoxicity.

## Possible mechanisms

Further stratification by any of the different herbs that had ever been reported as having such potential showed that *Radix Paeoniae* and *Radix Glycyrrhizae* might be involved (Table 3). In traditional Chinese medicine, *Radix Paeoniae* is used to be utilized for gynecological, gastrointestinal, and traumatic disorders. *Radix Glycyrrhizae* is used to enhance the effects and reduce toxicity of mixed CHMs and had a cytoprotective on to the liver in the cell culture study.[26] Although they were thought gentle and nontoxic, these two kinds of herbs have been reported as possible toxic components in patients with acute hepatitis[10,11] and the result of *in vitro* study should be confirmed by animal study and clinical trials. Our study provides the safety information for postmarketing surveillance of CHMs. In addition, there were variable latencies and no dose-response effect in our patients with nonviral, nonalcoholic hepatitis (Table 4).

In patients with HBV or HCV infections, injury to the liver has been reported to be more likely related to hepatotoxic medicines or herbs. But in our study, the odds ratios of both hepatitis B and C groups were not higher than those of nonviral, nonalcoholic hepatitis. Although it has been generally accepted that most cases of drug- and herb-induced hepatotoxicity are idiosyncratic,[8,27,28] the mechanism is complex. Part of idiosyncratic reaction is related to hypersensitivity or immunological response.[29] This immune mechanism of liver injury might be different in patients with HBV or HCV infection.[30,31] However, the hepatotoxic mechanisms and possible interactions with chronic HBV and HCV infection require further study.

## Potential limitations

Since we did not have direct access to any of the original clinical data, our study was necessarily limited to the more severe cases resulting in patient hospitalizations, which would undoubtedly result in underestimation of the true incidence rates, particularly with regard to those with only mild manifestations. The NHI pays for prescribed CHMs in concentrated extract form only, while herbal stores sell CHMs by prescriptions and some kinds of CHMs for foods according to the Pharmaceutical Affairs Law in Taiwan. Thus we could not ignore these social practices. After the implementation of NHI since 1995, we believe that the prescriptions of concentrated herbal extract from the NHI accounts for the majority of CHMs. However, herbs may also be used in foods or health food products. We presumed that these habits in patients might be unchanged in a short period (i.e. around 2 years), and that using a case-crossover design we could then eliminate this potential confounding. Finally, this study also presumed that all prescribed medications were ingested, which may well overestimate the actual dosage, as there was some degree of expected noncompliant patients.

# Conclusions

Our results provide additional safety information on the use of CHMs, with the finding that there is some increased risk of hospitalization relating to acute hepatitis among CHM users. However, small case numbers and possible exposure misclassification should be considered. Further studies to corroborate the

**Table 4** Assessment of causality between prescribed Chinese herbal and conventional medicines with suspected hepatotoxicity within the 30-day risk period and hospitalizations in the nonviral, nonalcoholic hepatitis group

| Sex | Age | Hospital stay (days) | Suspected hepatotoxic medicines | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Chinese herbal medicines | | | | Conventional medicines | | |
| | | | Days to event† | Prescription | Total dosage (g) | Mixed formulae | Days to event† | Prescription | Total dosage (mg) |
| M | 48 | 19 | 1–17 | *Radix Glycyrrhizae* | 4.3 | Du-Huo-Ji-Sheng-Tang | – | – | – |
| | | | | *Radix Paeoniae* | 4.3 | | | | |
| F | 46 | 25 | 2–9 | *Radix Scutellariae* | 14.1 | Chai-Ko-Chieh-Chi-Tang, Kan-Lu-Yin, Ko-Ken-Tang, | – | – | – |
| | | | | *Herba Ephedrae* | 15.8 | Sheng-Su-Yin, Pan-Hsia-Pai-Chu-Tien-Ma-Tang | | | |
| | | | | *Radix Paeoniae* | 18.8 | | | | |
| | | | | *Radix Glycyrrhizae* | 21.3 | | | | |
| | | | | *Radix Bupleuri* | 8.3 | | | | |
| | | | | *Rhizoma Atracylodis Macrocephalac* | 12.4 | | | | |
| M | 70 | 3 | 23–28 | *Radix Paeoniae* | 6.7 | Ching-Chieh-Lien-Chiao-Tang, | – | – | – |
| | | | | *Radix Scutellariae* | 22.7 | Huang-Lian-Chieh-Tu-Tang | | | |
| | | | | *Radix Bupleuri* | 6.7 | | | | |
| | | | | *Radix Glycyrrhizae* | 5.0 | | | | |
| M | 37 | 4 | 11–23 | *Radix Glycyrrhizae* | 2.3 | Du-Huo-Ji-Sheng-Tang, Huang-Chi-Wu-Wu-Tang | – | – | – |
| | | | | *Radix Paeoniae* | 12.3 | | | | |
| F | 40 | 3 | 0–5 | *Radix Glycyrrhizae* | 21 | Huang-Lian-Tang | – | – | – |
| F | 75 | 10 | 3–10 | *Radix Glycyrrhizae* | 19.4 | Chiu-Wei-Chiang-Huo-Tang | 0–2 | Sulfamethoxazole | 3200 |
| | | | | *Radix Scutellariae* | 19.4 | | | Felodipine | 10 |
| | | | | | | | | Cimetidine | 2500 |
| | | | | | | | | Mefenamic acid | 1500 |
| M | 65 | 9 | 5–22 | *Radix Glycyrrhizae* | 72.7 | Dang-Gui-Nian-Tong-Tang, | 1–5 | Cimetidine | 2400 |
| | | | | *Radix Paeoniae* | 26.3 | San-Tsung-Kuei-Chien-Tang, Kuei-Chih-Tang | | Sulindac | 1200 |
| | | | | *Radix Scutellariae* | 68.8 | | | Ibuprofen | 1600 |
| | | | | *Radix Bupleuri* | 15.6 | | | Piroxicam | 20 |
| | | | | *Rhizoma Atracylodis* Macrocephalac | 26.3 | | | | |
| M | 35 | 5 | 8–24 | *Radix Glycyrrhizae* | 1.6 | Cheng-Ku-Tzu-Chin-Tan, Bai-Shau | 3 | Ketoprofen | 50 |
| | | | | *Radix Paeoniae* | 79.0 | | | | |
| | | | | *Cortex Moutan* | 4.0 | | | | |
| M | 32 | 5 | 0–11 | *Radix Glycyrrhizae* | 14.0 | Chai-Hu-Shu-Kan-Tang | 0–2 | Lorazepam | 2 |
| | | | | *Radix Paeoniae* | 28.0 | | | | |
| | | | | *Radix Bupleuri* | 37.3 | | | | |
| F | 58 | 6 | 16–20 | *Radix Glycyrrhizae* | 29.7 | Ko-Ken-Tang, Qiang-Huo-Sheng-Shi-Tang | 14–17 | Prednisolone | 45 |
| | | | | *Radix Paeoniae* | 19.2 | | | | |
| | | | | *Herba Ephedrae* | 28.8 | | | | |
| M | 49 | 5 | – | None | – | – | – | Chlorzoxazone | 3000 |
| | | | | | | | | Piroxicam | 120 |
| M | 58 | 5 | – | None | – | – | – | None | – |

†Duration between the beginning of the prescription and hospitalization.

above findings are warranted in order to verify such hepatotoxicity and the potential interaction with viral hepatitis in Taiwan, where the carrier rates of both the HBV and HCV are particularly high.

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ORIGINAL REPORT

# Increased risk of hospitalization for acute hepatitis in patients with previous exposure to NSAIDs†

Chang-Hsing Lee[1,2], Jung-Der Wang[1,3,4] and Pau-Chung Chen[1]*

[1]*Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan*
[2]*Department of Occupational Medicine, Ton Yen General Hospital, Hsinchu County, Taiwan*
[3]*Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*
[4]*Department of Environmental and Occupational Medicine, National Taiwan University Hospital, Taipei, Taiwan*

## SUMMARY

**Background** Epidemiological studies related to hospitalization due to the hepatotoxicity of traditional non-steroidal anti-inflammatory drugs (NSAIDs) are infrequent, and case reports of hepatotoxicity of nimesulide, celecoxib, and rofecoxib seem to be increasing. The reimbursement database of National Health Insurance (NHI) in Taiwan provided an opportunity for post-marketing surveillance. We conducted this study to determine the association between the use of hepatoxic NSAIDs and increased hospitalizations related to acute hepatitis.

**Methods** We included hospitalized subjects with a major diagnosis of acute or sub-acute necrosis of liver or toxic hepatitis and excluded viral and other causes of hepatobiliary diseases from the NHI database from 1 April 2001 to 31 December 2004. We applied two kinds of models to analyze by uni-directional and bi-directional case-crossover designs during the 28 days exposure periods and performed conditional logistic regression models.

**Results** There were 4519 cases of hospitalization relating to acute hepatitis, and the odds ratios of celecoxib, nimesulide, dicofenac, ibuprofen, and other hepatoxic NSAIDs were significantly increased. Compared with the adjusted odds ratios of other hepatoxic NSAIDs (OR = 2.13, 95%CI = 2.00, 2.28), celecoxib (OR =1.92, 95%CI = 1.38, 2.69) was similar during the 28 days by our uni-directional case-crossover design.

**Conclusions** Our results provide evidence for an increased risk of hospitalization with acute hepatitis among hepatoxic NSAIDs including celecoxib users. Further mechanistic research is warranted in order to document celecoxib's hepatotoxicity. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — acute hepatitis; case-crossover design; cyclooxygenase 2 inhibitors; non-steroidal anti-inflammatory drugs

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## BACKGROUND

Drug-induced liver injury (DILI) is a common cause of acute non-viral nontoxic liver failure,[1] and liver damage is a major reason for withdrawal of a drug from the market.[2] In France, the incidence rate of outpatient DILI amounts to fourteen cases per 100 000 inhabitants, which is still considered as an underestimation because of difficulty in diagnosis.[3] Given its relatively rare incidence, DILI may not be detected in clinical trials with limited numbers of subjects. Therefore, increasing numbers of cases of hepatotoxicity may emerge after starting marketing when a sufficient number of patients have been exposed to the new drug.[4]

The epidemiologic studies related to hospitalization due to the hepatotoxicity of traditional non-steroidal anti-inflammatory drugs (NSAIDs) are limited and should be pursued further.[5] New NSAIDs, such as the cyclo-oxygenase-2 (COX-2) selective inhibitors, were recently developed for the treatment of chronic osteoarthritis and rheumatic arthritis and were considered to be free from gastrointestinal side effects.

* Correspondence to: P.-C. Chen, Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, 17 Syujhou Road, Taipei 10055, Taiwan. E-mail: pchen@ntu.edu.tw
† The authors have no conflicts of interest that are directly relevant to the content of this study.

Recently, case reports related to hepatotoxicity seem to be increasing in frequency for nimesulide,[6–8] celecoxib,[9–12] and rofecoxib.[13,14] However, a meta-analysis of clinical trials concluded that celecoxib has a low potential hepatotoxicity.[15] Another cohort study[16] and a case/non-case analysis[17] seemed to result in the same conclusion.

The National Health Insurance (NHI) program in Taiwan is a universal system of compulsory health insurance. It provides coverage for more than 96.2% of the population, and the proportions of contracted medical care institutions are about 96.5% of all hospitals and 89.5% of all clinics.[18] The NHI database contains virtually all of the health insurance, medical and prescription records for almost all citizens in Taiwan, which provides an opportunity for the post-marketing surveillance of new drugs. This study was therefore conducted in an attempt to determine the association between the use of hepatoxic NSAIDs, COX-2 selective inhibitors and the risk of hospitalizations relating to acute hepatitis.

## METHODS

### *Data source*

The dataset was obtained from the NHI database in Taiwan. The NHI files consist of comprehensive information on all medications prescribed to all insured individuals. We utilized both the outpatient visits and admission databases, which included information on gender, date of birth, date of admission, date of discharge, dates of visits, admission diagnoses, outpatient visit diagnoses, and prescription information (e.g., names, dosages, days, and expenditures). The Ethics Review Board at the National Taiwan University College of Public Health approved this study, with strict confidentiality guidelines being closely followed in accordance with personal electronic data protection regulations.

### *Study period and population*

Three COX-2 selective inhibitors (rofecoxib, celecoxib, and nimesulide) are commercially available in Taiwan. The NHI began to reimburse for celecoxib, rofecoxib, and nimesulide on 1 April 2001, 1 July 2001, 1 and March 2003, respectively, but rofecoxib was withdrawn from the market in October 2004 because of reports of cardiovascular events. For these reasons, we chose a study period that started on 1 April 2001 and ended on the last date in the database that we applied for, 31 December 2004. The number of people in the annual dataset for all publicly insured people ranged from 21 653 555 in 2001 to 22 134 270 in 2004.

In order to prevent any misclassification of case diagnoses, we selected the study population from all publicly insured people by using the major diagnosis at admission as the definition of each case instead of minor diagnoses of admission or any diagnoses from outpatient clinics. The diagnoses in the NHI database generally follow the International Classification of Diseases, 9th Revision (ICD-9) codes. We included only the diagnoses of acute and sub-acute necrosis of the liver (ICD-9 570) and toxic (noninfectious) hepatitis (ICD-9 573.3). We excluded patients diagnosed before admission with viral hepatitis A, B, C, or other viral hepatitis (ICD-9 070.0 to 070.9), viral hepatitis B or C carriers (ICD-9 V026.1 to V026.9), hepatitis in viral and other infectious diseases classified elsewhere (ICD-9 573.1 to 573.2), cholelithiasis (ICD-9 574.0 to 574.9), chronic liver disease and cirrhosis (ICD-9 571.0 to 571.9), liver abscess and sequelae of chronic liver disease (ICD-9 572.0 to 572.8), chronic passive congestion of liver (ICD-9 573.0), malignant neoplasm of liver and intrahepatic bile ducts (ICD-9 155.0 to 155.2), or liver metastasis (ICD-9 230.8). Because subjects might have been admitted more than once, we selected the earliest admission date for each individual.

### *Case-crossover design*

Since there are many determinants, or potential confounders, of acute hepatitis, we applied the case-crossover design proposed by Maclure[19] as a means of controlling for factors within subjects. Thus, there was no control selection bias since each case acted as its own control. In drug safety studies, the likelihood of prescribing a new medication may change over time.[20] To avoid any potential bias related to time trends, we have therefore adopted uni- and symmetrically bi-directional case crossover designs, which use the four prior and two prior–posterior symmetrical periods as controls.[21] The important consideration in this design was the overall length of the exposure time period, based on case or population history.[22] To make appropriate assumptions on the latent and induction times, we searched all of the available information on adverse effects from the case reports of celecoxib, rofecoxib, and nimesulide. Given that the latency period for conventional hepatoxic drugs ranges between 5 and 90 days[23] and any case occurring more than 15 day (for acute hepatocellular toxicity) or 30 days (for cholestasis) after drug withdrawal can be excluded, we decided to use 28 days as exposure windows to ensure that the treatment is not stopped



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more than 15 days before onset of hepatotoxicity.[24] Information was collected on prescriptions taken during each exposure window. In addition, given that transaminase elevation in case reports usually recovered within 14 days to 4 months, 90 days was selected as the washout period. For example, four prior control periods were selected, with exposure times beginning at 118, 236, 354, and 472 days prior to the date of admission. In the same way, two prior control and two later control periods were selected, beginning at 118 days and 236 days before and after the date of admission (Figure 1). In brief, there were two kinds of models to analyze by uni-directional and bi-directional case-crossover designs during the 28 days periods. After comparing the results of the two models, we selected the model with the uni-directional case-crossover design for further sensitivity analysis.

*Exposures of interest and covariates for adjustment*

Furthermore, we undertook a search of the Micromedex® database for drugs reported as having any connection with hepatotoxicity.[25] A total of 702 generic drugs were found, and the NHI in Taiwan regularly reimbursed 270 of them. We grouped them by anatomical therapeutic chemical (ATC) code and used them for adjustment. For example, if the ATC codes were M01AB, M01AC, M01AE, M01AG, M01AX, M02AA, N02BA, and B01AC, we classified these 26 drugs as 'hepatoxic NSAIDs'; J01 as 70 'antibacterial drugs'; J04A as 5 'anti-tuberculosis drugs'; N02CA, N03AA, N03AE, N05BA, and N05CD as 14 'benzodiazepine and barbiturate drugs'; and the residues as 155 'other hepatoxic drugs'. Also, there were reports of hepatotoxicity from using Chinese herbal medicines.[26,27] Therefore, prescriptions of Chinese herbal medicines were grouped as 'Chinese herbs'.

We selected the two most frequent traditional NSAIDs (diclofenac and ibuprofen), three COX-2 selective inhibitors (celecoxib, rofecoxib and nimesulide) and other hepatoxic NSAIDs (21 hepatoxic NSAIDs, excluding the previous five drugs) to compare the odds ratios between them.

However, in order to investigate the condition of celecoxib prescription during the study period, we further observed the characteristics, prescribing frequencies and patterns of the cases that had celecoxib prescriptions in the risk period and the number of prescriptions for celecoxib taken all subjects per year. To clarify the dose–response relationship between the COX-2 selective inhibitors and hospitalization, we compared the daily doses of prescriptions on the date closest to admission and cumulative doses during the risk period.

## SENSITIVITY ANALYSIS AND EXTERNAL ADJUSTMENT FOR UNMEASURED CONFOUNDERS

Finally, we carried out three sets of sensitivity analyses to test the robustness of our findings. First, if we defined 28-day risk and control periods by using a case-crossover design as mentioned before, not all subjects could be included in a 1-to-4 match uni-directional case-crossover design for lack of control periods during the study period. In addition, some individuals had further records in our study databases after admission. Furthermore, some subjects might have used celecoxib but stopped after admission. According to these different prescribing patterns, we stratified the sample according to these subgroups. Second, sex, older age, and the status of diseases may affect DILI.[4] Common approved indications for treatment with celecoxib and rofecoxib were osteoarthritis (ICD-9 715) and rheumatoid arthritis (ICD-9 714.0, 714.3). Then, we explored the data for any of the following conditions or co-morbidities before admission for acute non-viral hepatitis: diabetes mellitus (ICD-9 250), essential hypertension (ICD-9 401), obesity and hyperlipidemia (ICD-9 272, 278), chronic kidney disease and renal failure (ICD-9 585 to 586), hyperthyroidism (ICD-9 242), fasting and malnutrition (ICD-9 260 to 263), or neoplasms (ICD-9 140 to 239). Pregnancy (ICD-9 646.7, V72.40 to 72.42, V22.0 to 22.2) was also considered for 300 days before admission. We stratified the total population into

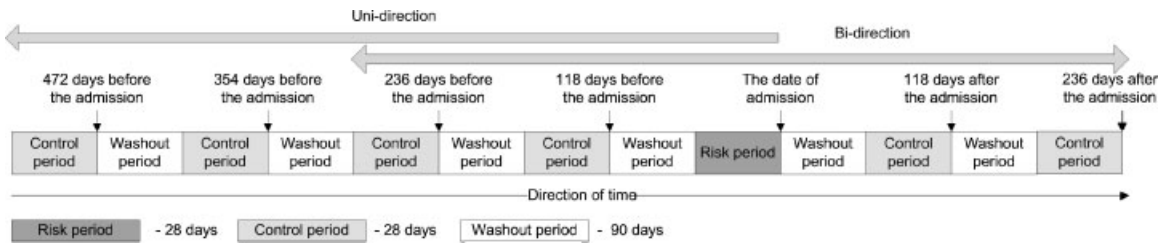


Figure 1. Timeline of the risk and four uni- and bi-directional control periods



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subgroups according to the three co-morbidities that were diagnosed most frequently. Third, we grouped the hepatoxic drugs into classes to adjust for the fact that some specific drugs within a class might be hepatoxic. We also stratified them into subgroups according to the seven most frequent co-prescriptions that were used by our subjects during the study period.

### *Data analysis*

Since the design of this study utilized one case period matched with four control periods, we analyzed the data through construction of conditional logistic regression models to explore the association between hospitalization and prescriptions while controlling for antibiotics, anti-tuberculosis drugs, benzodiazepines, and barbiturates, Chinese herbs and other hepatoxic drugs. We then calculated odds ratios and 95% confidence intervals (CIs). The analysis of the data was performed using SAS version 9.13 software (SAS Institute Inc., Cary, NC).

## RESULTS

From the data on all insured individuals from the Taiwan NHI database between 1 April 2001 and 31 December 2004, there were a total of 15 088 subjects who conformed to the inclusion criteria. Among them, 1568 admitted cases were excluded in order to allow for the risk period and at least one control period during the study period. Otherwise, based on the exclusion criteria, another 9001 subjects who were diagnosed as viral and other causes of hepatobiliary diseases were excluded. Of the remaining 4519 cases, 69.6% of the individuals were 15–64 years of age, with a mean age of $46.1 \pm 21.7$ years. If we defined 28-day time windows by using a uni-directional case-crossover design, the total numbers of subjects that could be matched for 1-to-1, 1-to-2, 1-to-3, and 1-to-4 were 416, 443, 515, and 3145, respectively. In addition, 98 individuals had no further records in either the inpatient or admission databases or were assumed to have died during the relevant hospitalization. The five most common co-morbid diseases before admission were essential hypertension (21.0%), osteoarthritis (14.5%), diabetes mellitus (14.0%), neoplasms (13.9%), and obesity and hyperlipidemia (11.1%). There were 35, 19, and 30 subjects who had been prescribed celecoxib, rofecoxib, and nimesulide, respectively, within the 28-day risk period, as summarized in Table 1.

Moreover, we explored 35 cases that had celecoxib prescriptions in the 28-day risk period. Their mean age was $60.9 \pm 20.0$ years, and 23 cases were females.

Table 1. Characteristics, co-morbidities, and hepatoxic co-prescriptions of study subjects with initial admission diagnosis of acute non-viral hepatitis, 2001–2004

| Characteristics | No. | % |
|---|---|---|
| Total | 4519 | 100.0 |
| Sex | | |
| Male | 2580 | 57.1 |
| Female | 1939 | 42.9 |
| Age | | |
| <15 years | 332 | 7.3 |
| 15–64 years | 3143 | 69.6 |
| ≥65 years | 1044 | 23.1 |
| Co-morbidities that may enhance susceptibility | No.* | % |
| Essential hypertension | 951 | 21.0 |
| Osteoarthritis | 653 | 14.5 |
| Diabetes mellitus | 631 | 14.0 |
| Neoplasms | 626 | 13.9 |
| Obesity and hyperlipidemia | 501 | 11.1 |
| Chronic kidney disease and renal failure | 255 | 5.6 |
| Hyperthyroidism | 80 | 1.8 |
| Rheumatoid arthritis | 67 | 1.5 |
| Systemic lupus erythematosus | 39 | 0.9 |
| Fasting, malnutrition | 37 | 0.8 |
| Pregnancy | 25 | 0.6 |
| Prescriptions | No.† | % |
| Celecoxib | 35 | 0.8 |
| Rofecoxib | 19 | 0.4 |
| Nimesulide | 30 | 0.7 |
| Diclofenac | 580 | 12.8 |
| Ibuprofen | 287 | 6.4 |
| Other hepatoxic NSAIDs ‡ | 1487 | 32.9 |
| Co-prescriptions | No.† | % |
| Chinese herbs | 261 | 5.8 |
| Antibacterial drugs | 735 | 16.3 |
| Anti-tuberculosis drugs | 112 | 2.5 |
| Benzodiazepine and barbiturates | 499 | 11.0 |
| Other hepatoxic drugs | 1687 | 37.3 |

NSAIDs, non-steroidal anti-inflammatory drugs.
*Each subject might have any number of co-morbidities before admission.
†Each subject might have any number of prescriptions and co-prescriptions during the 28-day risk period.
‡Other hepatoxic NSAIDs: all hepatoxic NSAIDs except celecoxib, rofecoxib, nimesulide, diclofenac, and ibuprofen

Mean percentage of all prescription days divided by total days from 1 April 2001 to admission date was $17.5 \pm 22.2\%$. Fifteen cases stopped celecoxib after admission. We also found that the number of prescriptions for celecoxib taken by 4519 cases per year increased from 99 to 650 between 1 April 2001 and 31 December 2004.

In Table 2, it is shown that the odds ratios of all NSAIDs significantly increased during the 28 days by uni-directional designs. The odds ratios yielded by uni-directional designs were also larger than those obtained by bi-directional designs. Compared with the adjusted odds ratios of other hepatoxic NSAIDs (OR = 2.13, 95%CI = 2.00, 2.28), nimesulide (OR = 2.63, 95%CI = 1.83, 3.77) seemed slightly larger, but celecoxib's (OR = 1.92, 95%CI = 1.38, 2.69) was similar by

Table 2. Adjusted odds ratios of COX-2 selective inhibitors, diclofenac, ibuprofen, and other hepatoxic NSAIDs on hospitalizations with acute non-viral hepatitis during the 28 days of the risk period with prior and posterior control periods, 2001–2004

| | | Cases ($N=4519$) | Prior controls | | | | Prior and posterior controls | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Controls ($N=15\,427$) | OR* | 95%CI | | Controls ($N=16\,670$) | OR* | 95%CI | |
| Celecoxib | | 35 | 63 | 1.92 | 1.38 | 2.69 | 73 | 1.71 | 1.23 | 2.39 |
| Daily dose† | ≥200 mg | 28 | 53 | 1.86 | 1.28 | 2.71 | 63 | 1.63 | 1.12 | 2.36 |
| | <200 mg | 7 | 10 | 2.20 | 1.04 | 4.64 | 10 | 2.17 | 1.03 | 4.58 |
| Cumulative dose‡ | ≥2000 mg | 25 | 51 | 1.77 | 1.19 | 2.63 | 55 | 1.65 | 1.11 | 2.45 |
| | <2000 mg | 10 | 12 | 2.45 | 1.31 | 4.58 | 18 | 1.89 | 1.01 | 3.52 |
| Rofecoxib | | 19 | 45 | 1.60 | 1.01 | 2.51 | 66 | 1.18 | 0.75 | 1.85 |
| Nimesulide | | 30 | 31 | 2.63 | 1.83 | 3.77 | 42 | 2.19 | 1.53 | 3.15 |
| Diclofenac | | 580 | 794 | 2.22 | 2.05 | 2.42 | 889 | 2.06 | 1.90 | 2.24 |
| Ibuprofen | | 287 | 318 | 2.51 | 2.23 | 2.82 | 383 | 2.24 | 1.99 | 2.52 |
| Other hepatoxic NSAIDs§ | | 918 | 1350 | 2.13 | 2.00 | 2.28 | 1594 | 1.91 | 1.78 | 2.04 |

COX-2, cyclo-oxygenase-2; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; CI, confidence interval.
*Adjusted for antibacterial drugs, anti-tuberculosis drugs, benzodiazepines, and barbiturates, Chinese herbs and other hepatoxic drugs.
†Daily doses of prescriptions on the date closest to admission.
‡Cumulative doses of prescriptions during the risk period.
§Other hepatoxic NSAIDs: all hepatoxic NSAIDs except celecoxib, rofecoxib, nimesulide, diclofenac, and ibuprofen.

uni-directional designs. There appeared to be no significant dose–response relationship for celecoxib when we stratified the daily doses into above or below 200 mg/day or cumulative doses into above or below 2000 mg. The number of subjects with larger daily doses or cumulative doses was too small to be stratified in the analyses of rofecoxib and nimesulide.

The sensitivity analysis for the 28-day risk period in the uni-directional design is summarized in Table 3. We did not find any apparent changes in subgroups of sex, age, different matched patterns, prescribing conditions, three common co-morbidities, or seven potentially hepatoxic co-prescriptions.

Table 3. Sensitivity analysis of adjusted odds ratios between hospitalizations with acute non-viral hepatitis and celecoxib stratified by subgroups with sex, age, different matched patterns, prescribing conditions, co-morbidities, and co-prescriptions during the 28 days of the risk period with four prior control periods

| Models | Items | Cases | Controls | OR* | 95%CI | |
|---|---|---|---|---|---|---|
| Main model | Total population | 35 | 63 | 1.92 | 1.38 | 2.69 |
| Subgroup effects | | | | | | |
| Sex | Male | 13 | 27 | 1.73 | 1.00 | 3.00 |
| | Female | 22 | 36 | 2.05 | 1.35 | 3.13 |
| Age | <65 years | 15 | 15 | 2.70 | 1.62 | 4.51 |
| | ≥65 years | 20 | 48 | 1.54 | 0.99 | 2.40 |
| Matched patterns | One risk to one control periods | 2 | 1 | 3.68 | 0.90 | 14.99 |
| | One risk to two control periods | 0 | 1 | — | — | — |
| | One risk to three control periods | 1 | 1 | 2.57 | 0.36 | 18.57 |
| | One risk to four control periods | 32 | 60 | 1.88 | 1.32 | 2.67 |
| Prescribing conditions | Stop celecoxib after admission | 15 | 3 | 4.60 | 2.74 | 7.74 |
| | Die after admission | 4 | 6 | 2.13 | 0.79 | 5.74 |
| Co-morbidities† | Essential hypertension | 18 | 43 | 1.55 | 0.97 | 2.47 |
| | Diabetes mellitus | 12 | 23 | 1.81 | 1.02 | 3.22 |
| | Osteoarthritis | 17 | 43 | 1.50 | 0.93 | 2.42 |
| Co-prescriptions‡ | Chlorzoxazone | 21 | 50 | 1.58 | 1.03 | 2.43 |
| | Sulfamethoxazole | 23 | 37 | 2.05 | 1.36 | 3.11 |
| | Amlodipine | 12 | 24 | 1.77 | 1.00 | 3.13 |
| | Allopurinol | 6 | 13 | 1.69 | 0.75 | 3.79 |
| | Metformin | 9 | 19 | 1.70 | 0.88 | 3.30 |
| | Rifampin | 5 | 6 | 2.51 | 1.03 | 6.08 |
| | Isoniazid | 3 | 4 | 2.42 | 0.77 | 7.63 |

OR, odds ratio; CI, confidence interval.
*Adjusted for Chinese herbs and other hepatoxic medications.
†Diseases may affect hepatotoxicity.
‡Potential hepatoxic co-prescriptions.



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## DISCUSSION

Our study found that nimesulide, dicofenac, ibuprofen, and other hepatoxic NSAIDs increased the risk of hospitalization for acute hepatitis, which corroborates previous studies. Moreover, there was a significantly higher risk in the use of celecoxib, which has never been reported before.[15–17] Before drawing any conclusions, we should carefully evaluate any alternative explanations.

To prevent potential bias by misdiagnosis, we deliberately included only patients who were hospitalized and excluded other possible causes of hepatobiliary diseases, including all hepatitis related to infection, alcohol, cholelithiasis and de-compensated hepatic conditions, as these predisposed conditions might more likely lead to liver injury from potential hepatoxic drugs. Thus, our estimates were more conservative because we did not include the above cases. Since we did not have any direct access to original clinical data, our study was necessarily limited to the more severe cases resulting in hospitalizations, which undoubtedly results in underestimation of hepatotoxicity with only mild manifestations.

The higher risk during 28 days observed by uni-directional design might be related to acute hepatotoxicity of celecoxib, such as in the patients who were previously sensitized to the drugs.[11,23] Otherwise, we speculate that the increased risk may be partly due to confounding by indication according to the trend by sensitivity analysis of time windows. It is usually influenced by several factors, such as physician's decision, severity of the disease, concomitant medical conditions, and therapy.[28]

We also used bi-directional design to reduce time trend bias of celecoxib and risk of celecoxib users was smaller but significantly high still. The risk of taking the same medication might disappear after the correct diagnosis of DILI is made. A higher odds ratio for those who had stopped taking celecoxib after admission also supported our conjecture. Thus, our bi-directional design might underestimate the true risk.

Our results also corroborate the evidence that the risk of hospitalizations for hepatopathy among users of nimesulide was higher than for those using other hepatoxic NSAIDs.[16,17] On the other hand, there seemed to be a slightly higher toxicity for celecoxib in our study compared to those conducted in Western countries.[15,29] Our analysis showed that the 35 cases exposed to celecoxib were much older and more commonly female than the overall case population. Besides, Table 3 reveals female patients, with less than 65 years had higher risk in this population. Moreover, these factors, with racial differences, may be associated with susceptibility[30] to DILI. However, these factors should be already adjusted by the case-crossover design.

In addition, odds ratios adjusted by either daily or cumulative dose during the risk period did not show any dose–response relationship. This observation appears to conform to the findings of idiosyncratic DILI.[31]

We conducted further sensitivity analyses by stratification to clarify the misclassifications and potential confounders. Table 3 reveals no valuable changes in the odds ratios of the subgroups with sex, age, different prescribing conditions, matched patterns, and co-morbidities. While the medications being studied were co-prescribed with seven potential hepatoxic drugs, the results reveal that there were no dramatic contributions of drug–drug interactions.

Potential limitations of unmeasured confounders, patient compliance, and use of other out-of-pocket drugs should also be discussed. First, we applied a case-crossover design to control for unmeasured confounders, such as personal constitution and lifestyle factors. Second, although the reimbursement data used in this study cannot provide information on actual intake of prescribed medication, such a limitation usually leads toward random misclassification and an under-estimation of risk. Finally, our NHI covers comprehensively almost all kinds of medications, except for unproven new chemotherapeutic drugs; our subjects rarely paid to purchase additional medications.

Our results provide additional safety information for the use of celecoxib as well as hepatoxic NSAIDs, with the finding that there was an increased risk of hospitalization for acute hepatitis. Further mechanistic research is warranted for celecoxib's hepatotoxicity.

### KEY POINTS

- The first pharmacoepidemiologic study by using the case-crossover design in the database survey the hepatotoxicity of new drugs in the real world.
- The results provide evidence for an increased risk of hospitalization with acute hepatitis among nimesulide, dicofenac, ibuprofen, and hepatoxic NSAIDs especially including celecoxib users.
- The risk of celecoxib's hepatotoxicity is higher than the results of previous studies in the western countries.
- The study provides additional safety information for the use of celecoxib.




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