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The association of peptic ulcer and schizophrenia: A population-based study

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ABSTRACT

Background: The association of schizophrenia with peptic ulcer is not conclusive. In the last 30 years, there has been little evaluation of peptic ulcer among schizophrenia patients.
Methods: To explore the relation of peptic ulcer and schizophrenia during this new phase, we used the data from Taiwan insurance claims, identified 1496 schizophrenia patients (ICD-9-CM: 295) and selected 5984 non-schizophrenia controls that were frequency-matched by sex, age, and index year with schizophrenia patients during the years 1998–2001. All subjects were free of peptic ulcer at baseline. We measured incidences of peptic ulcer (ICD-9-CM: 531–534) until the end of 2009.
Results: The incidence of peptic ulcer was 1.27 times higher in schizophrenia patients than in the control group (12.1vs. 9.52 per 1000 person-years). Patients are at higher risk taking anti-depression, anxiolytic and hypnotics or non-steroidal anti-inflammatory drugs. After controlling the confounding factors, schizophrenia patients had no significant increase incidence of peptic ulcer.
Conclusion: Schizophrenia patients have a slightly higher risk of peptic ulcer compared to the general population. This might be due to a higher rate of taking anti-depression, anxiolytic and hypnotics or non-steroidal anti-inflammatory drugs and alcoholism among this group.

Introduction

Schizophrenia is a chronic and disabling psychiatric disorder with a worldwide prevalence of approximately 1% [1]. Patients with schizophrenia have been reported to have a higher mortality rate due to physical illness than the general population [2–4]. Although these patients have been reported to have a higher risk of several physical illnesses [5,6], there are few reports about the association between schizophrenia and peptic ulcer, and these reports are not conclusive [7]. Peptic ulcer is a common digestive system disease with a prevalence of around 10–15% [8,9]. There are multiple possible risk factors of peptic ulcer reported, including *Helicobacter pylori* (*H. pylori*) infection, alcohol, smoking and nonsteroidal anti-inflammatory drugs (NSAIDs) Schizophrenic patients were found to have a higher rate of *H. pylori* infection [10], which is one of the important factors contributing to peptic ulcer. They were also found to have a high prevalence of dyspepsia [11]. Schizophrenia patients also have higher risk of alcohol abuse and smoking [12–14], which could attribute to peptic ulcer. On the other hand, schizophrenia is caused partially by a hyperactivity of dopaminergic system [15]. Dopamine system was documented having a protective effect toward peptic ulcer [16–20]. There was an observational study based on in-patients' database showed that schizophrenia patients had lower risk than the general population [21]. The results was limited with the source of patients, which were included with in-patients. There has been little finding about the association between peptic ulcer and schizophrenia in the recent decades.

The incidence of peptic ulcer related to *H. pylori* infection has declined in recent decades [22,23], but the risk of peptic ulcer among schizophrenic patients might be different. Besides, schizophrenia patients might take antipsychotic agents to control their psychotic symptoms. Antipsychotics included dopamine receptor antagonist,

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which might decrease the protective effect of dopamine agonist [24]. The aim of this study is to investigate the risk of peptic ulcer among patients with schizophrenia compared with the general population. Medications were considered as covariates in this study. In addition, this is the first population-based study to investigate peptic ulcer diagnosed by endoscopy among schizophrenic patients.

Method

Data sources and study subjects

The Taiwan National Health Insurance program, which covers over 23.03 million residents, or about 99.2% of the Taiwan population, was reformed on March 1, 1995, by the Bureau of National Health Insurance (BNHI). BNHI has released scrambled data to the National Health Research Institutes (NHRI) to establish 18 National Health Insurance Research Databases (NHIRDs) (http://w3.nhri.org.tw/nhird/date_01.html). The Longitudinal Health Insurance Database (LHID2000) we used in this study included all the medical information of 1 million insurants randomly selected among beneficiaries during the period 1996–2000. There were no significant differences in the distribution of gender and age between the original claims data and the sampling data. The claims data in the LHID2000 was extended to December 31, 2009, and retrospectively collected until January 1, 1996. The diagnosis codes in the NHIRD were in accordance with those in the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). NHRI had scrambled patient identifications with surrogate numbers to secure patient privacy. The present study was approved by the ethic committee at China Medical University and Hospital.

The dataset comprised 1874 patients with newly diagnosed schizophrenia (ICD-9-CM: 295) during the years 1998–2001; the date of schizophrenia diagnosis was the index date. We excluded patients who had gastrointestinal ulcers (ICD-9-CM: 531–534) diagnosed before schizophrenia was diagnosed ($n = 378$); in all, 1496 patients were selected as the schizophrenia group. For comparison, we randomly selected people without a history of schizophrenia and peptic ulcer. These controls were frequency-matched by age, sex and index year with the cases in the corresponding schizophrenia cohort, with a control sample size four-fold of the corresponding schizophrenia cohort. We measured incidences of peptic ulcer (ICD-9-CM: 531–534) until the end of 2009 and the diagnosis was checked by the prescription of H2-blocker and prompt-pump inhibitors (PPI).

We also considered potentially confounding variables, including urbanization levels, monthly income, alcoholism, depression, bipolar, anxiety and medicine prescription history. The NHRI divided the urbanization of Taiwan into 7 levels, with level 1 reflecting the most urbanized and level 7 the least [25]. We collapsed levels 5–7 into level 5 because there were few schizophrenic patients in those levels. The monthly income level cut-off was based on insurance fee level. Medicine prescription history included the prescription of antipsychotics, aspirin, lithium, valproate sodium, antidepressives, anxiolytics and hypnotics, and NSAIDs, which were identified within 180 days before the end-point, that is, the date of diagnosed gastrointestinal ulcer, death or failure to follow-up, or the end of 2009. The cumulative days of prescription were counted as the sum of days of use within 180 days before the end point.

Statistical analysis

The SAS 9.1 statistical package (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses in this study, and the significance level was set at 0.05. The chi-square test and t-test were used to determine any differences in sociodemographics and medical history between the two groups. We calculated the incidence rate ratio (IRR) and 95% confidence intervals (95% CI) for each variable of the two groups using Poisson regression. The disease-free rate and the differences in risk between the two groups were estimated with the Kaplan–Meier method and the log-rank test. The Cox proportional hazards model was used to assess the hazard ratios (HR) of gastrointestinal ulcers by covariates. Model 1 was adjusted sociodemographics (included sex, age, urbanization level, monthly income), alcoholism (ICD-9-CM: 305.0), depression (ICD-9-CM: 296.2, 296.3, 300.4 and 311), bipolar (ICD-9-CM: 296.0–296.1, 296.4–296.9) and anxiety (ICD-9-CM: 300.0, 300.2, 300.3, 308.3 and 309.81). Model 2 was adjusted sociodemographics, alcoholism, and medications, including aspirin, lithium, valproate sodium, antidepressives, anxiolytics and hypnotics, and non-steroidal anti-inflammatory drugs (NSAIDs). In further analysis, we also assessed the association for peptic ulcer between schizophrenia and antipsychotics used within 180 days before the end point. Data analysis considered also the risk associated the length of medication for NSAIDs. The joint effects for ulcer among antipsychotics, lithium, anti-depression and anxiolytics between two cohorts were estimated.

Results

We sampled 7480 subjects in all, 1496 in the schizophrenia group and 5984 in the non-schizophrenia group. There were more male schizophrenic patients (males 55.0% vs. females 45.0%) and the mean age was 36.5 years (SD = 15.8). Compared with the non-schizophrenia group, schizophrenic patients lived in areas with lower urbanization, had lower income, and a higher prevalence of alcoholism, depression, bipolar, anxiety and received more medication (including antipsychotics, aspirin, lithium, valproate sodium, antidepressives, anxiolytics and hypnotics, and NSAIDs) (Table 1). In the 12-year study period, the incidence of gastrointestinal ulcers in the schizophrenia group was 27% higher than in the non-schizophrenia group (12.1 vs. 9.54per 1000 person-years) (Table 2). The rate of receiving treatment of *H. pylori* eradication after the diagnosis of peptic ulcer in schizophrenia patients was lower than comparisons (7.64% vs. 14.4%,

Table 1
Baseline characteristics of schizophrenia and non-schizophrenia groups in 1998–2001

Variables	Schizophrenia				*p*-value
	No ($n = 5984$)		Yes ($n = 1496$)		
	n	%	*n*	%	
Sex					1.00
Women	2692	45.0	673	45.0	
Men	3292	55.0	823	55.0	
Age, years					1.00
≤20	772	12.9	193	12.9	
21 to ≤34	2492	41.6	623	41.6	
35 to ≤44	1252	20.9	313	20.9	
45 to ≤64	1064	17.8	266	17.8	
≥65	404	6.75	101	6.75	
Mean (SD)[a]	36.4	(16.0)	36.5	(15.8)	0.85
Urbanization level[b]					<0.0001
1	1812	30.3	421	28.1	
2	1756	29.3	394	26.3	
3	1154	19.3	304	20.3	
4	755	12.6	195	13.0	
5	507	8.47	182	12.2	
Monthly income (NTD)					<0.0001
0	370	6.18	136	9.09	
1 to ≤15,839	1659	27.7	692	46.3	
15,840 to ≤22,800	2643	44.2	545	36.4	
>22,800	1312	21.9	123	8.22	
Baseline comorbidity					
Alcoholism	9	0.15	50	3.34	<0.0001
Depression	26	0.43	139	9.29	<0.0001
Bipolar	9	0.15	128	8.56	<0.0001
Anxiety	45	0.75	109	7.29	<0.0001
Medicine history[c]					
Antipsychotics	22.5	3.76	1164	77.81	<0.0001
Aspirin	415	6.94	136	9.09	0.004
Lithium	5	0.08	154	10.3	<0.0001
Valproate sodium	38	0.64	264	17.7	<0.0001
Antidepressives	235	3.93	521	34.8	<0.0001
Anxiolytics and hypnotics	739	12.4	867	58.0	<0.0001
NSAIDs	3482	58.2	982	65.6	<0.0001

[a] Chi-square test, Student *t*-test.
[b] 1 indicates the highest level of urbanization and 5 the lowest.
[c] Medication used within 180 days before end point.