Mortality of Neuroleptic Malignant Syndrome Induced by Typical and Atypical Antipsychotic Drugs: A Propensity-Matched Analysis From the Japanese Diagnosis Procedure Combination Database

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ABSTRACT

Objective: Neuroleptic malignant syndrome induced by atypical antipsychotics presents atypical clinical manifestations with fewer symptoms compared with neuroleptic malignant syndrome induced by typical antipsychotics. However, any differences in prognosis between these 2 types of drug-induced neuroleptic malignant syndrome remain unknown. We examined neuroleptic malignant syndrome–related mortality in patients treated with typical or atypical antipsychotics by using a national administrative claims database.

Method: Data of patients with a diagnosis of neuroleptic malignant syndrome between July and December in each of the 5 years from 2004 to 2008 were extracted from the Japanese Diagnosis Procedure Combination database. Data included patient background, use of antipsychotics, and in-hospital mortality. Propensity score matching was performed to formulate a balanced 1:1 matched study and to compare in-hospital mortality between neuroleptic malignant syndrome patients taking typical antipsychotics and those taking atypical antipsychotics.

Results: We identified 423 neuroleptic malignant syndrome patients treated with typical antipsychotics and 215 neuroleptic malignant syndrome patients treated with atypical antipsychotics. Matching based on propensity scores produced 210 patients in each drug group. In-hospital mortality was substantially lower in the atypical antipsychotic group compared with the typical antipsychotic group, but the difference was not significant (3.3% vs 7.6%; OR = 0.44; 95% CI, 0.17–1.11; $P = .084$).

Conclusions: The results show that neuroleptic malignant syndrome remains a life threatening disease among patients receiving antipsychotics. A tendency for lower mortality in the atypical antipsychotic group may reflect differences in the pathophysiology. However, to clarify whether there is a difference in neuroleptic malignant syndrome–related mortality with the 2 types of antipsychotics, further studies with larger samples are needed.

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Neuroleptic malignant syndrome is a rare but potentially fatal adverse effect of antipsychotic medication. Although the pathophysiology of this lethal disease remains unclear, blockade of the D_2 dopamine receptor has been suggested to play a principal role.[1] It is well known that the use of typical antipsychotic drugs is associated with the occurrence of neuroleptic malignant syndrome.[2] Recently, the use of atypical antipsychotic drugs has become widespread for the first-line treatment of schizophrenia or other psychiatric symptoms. In Japan, the atypical antipsychotic risperidone became available in 1996; olanzapine, quetiapine, perospirone, aripiprazole, and blonanserin between 2001 and 2008; and clozapine in 2009. Atypical antipsychotics not only block D_2 receptors but also affect other receptors, including D_4, 5-hydroxytryptamine-1A (5-HT_{1A}) and -2C (5-HT_{2C}), and α-adrenergic receptors.[3] Limited evidence indicates that atypical antipsychotics also induced neuroleptic malignant syndrome but that the clinical manifestations of neuroleptic malignant syndrome induced by atypical antipsychotics were often "atypical."[3–7] A previous literature review[4] suggested that neuroleptic malignant syndrome induced by atypical antipsychotics might be associated with lower mortality than neuroleptic malignant syndrome induced by typical antipsychotics. However, the available data on mortality of patients with the syndrome were based on studies with small sample sizes, and a much larger sample is required to investigate whether there is any difference in mortality in neuroleptic malignant syndrome induced by typical and atypical antipsychotics.

In the present study, we used a national inpatient database to collect data from a large number of neuroleptic malignant syndrome patients and compared mortality between patients treated with typical or with atypical antipsychotics.

METHOD

Data Source

The Japanese Diagnosis Procedure Combination (DPC) database is a national database of general hospital patients in Japan and contains administrative claims data and discharge information of acute care inpatients.[8,9] The database includes the following data: type of hospital (teaching or nonteaching); patients' age and sex; diagnoses and comorbidities classified by *International Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) codes; procedures; drugs and devices used; and discharge status. The database started with 82 teaching hospitals in 2002, and the number of participant hospitals gradually increased each year to include 852 in 2008. Data were collected over 6 months (from July 1 to December 31) each year. In 2008, data from approximately 2.9 million inpatients (in all disciplines, including nonpsychiatric and psychiatric) were collected, representing approximately 40% of all acute care inpatient hospitalizations in Japan.

Clinical Points

- Clinicians can predict the prognosis of neuroleptic malignant syndrome in accordance with the causative drugs and with patient background and comorbidities.
- Clinicians should pay attention to the possibility of neuroleptic malignant syndrome in all age groups while treating with antipsychotics.

In Japan, many general hospitals have a psychiatric department that provides patients with acute and postacute care, while psychiatric hospitals mainly provide long-term care for patients with chronic disease. The DPC database includes data from general hospitals but not from psychiatric hospitals. As of 2008, the number of psychiatric beds was 8,221 in DPC hospitals and 15,669 in all the general hospitals in Japan; the coverage rate of the DPC was 56% of general hospitals.

This study was based on a secondary analysis of the administrative claims data. Because of the anonymous nature of the data, the requirement for informed consent was waived. Study approval was obtained from our institutional review board.

Descriptive Statistics

Data for this survey were extracted from the DPC database for the years 2004 to 2008. We identified records of all patients who had a diagnosis of neuroleptic malignant syndrome (*ICD-10* code G210). We collected information on type of hospital, patients' age, sex, use of antipsychotics, psychiatric diagnoses and comorbidities, the use of therapeutic drugs (dantrolene or bromocriptine), use of hemodialysis or tracheal intubation, use of electroconvulsive therapy, presence of intensive care unit (ICU) admission, and in-hospital mortality. We performed univariate comparisons of patient characteristics and in-hospital mortality using the χ^2 test.

Propensity Score Analysis for Mortality Comparison

First, we identified typical or atypical antipsychotic use among all the neuroleptic malignant syndrome patients. We checked each patient's records of antipsychotic prescriptions in the administrative claims data. Because the DPC database includes only inpatient data, prescription data in outpatient clinics were unavailable. Second, for comparison of in-hospital mortality between typical and atypical antipsychotic users, we used a propensity score analysis to adjust for differences in baseline characteristics.[10] We divided patients into 2 groups: a group treated with typical antipsychotics and a group treated with atypical antipsychotics alone. We performed a 1-to-1 matching between the groups on the basis of estimated propensity scores of each patient. The log odds of the probability of receiving a typical or atypical antipsychotic was modeled for potential confounders, including age, sex, comorbidities, and type of hospital. The C statistic for evaluating the goodness of fit was calculated. The estimated propensity scores were compared between the typical and atypical antipsychotic users, and a match occurred when 1 patient in the typical antipsychotic user group had an estimated propensity score within 0.6 standard deviation (SD) of another patient in the atypical antipsychotic user group. If 2 or more patients in the typical antipsychotic user group met this criterion, we randomly selected 1 patient for matching. Fisher exact test was used to compare in-hospital mortality between the propensity-score–matched groups of typical and atypical antipsychotic users. A logistic regression analysis was performed to analyze concurrent effects of various factors. The threshold for significance was a P value $< .05$. All statistical analyses were conducted using SPSS version 17.0 (SPSS, Chicago, Illinois).

RESULTS

Descriptive Statistics

Of 12 million inpatients in the database, 1,585 patients (384 in teaching hospitals and 1,201 in nonteaching hospitals) were identified with a diagnosis of neuroleptic malignant syndrome during the survey period. Mean ± SD age was 59.2 ± 17.9 years, and 912 patients (57.5%) were male. Regarding primary diagnoses, 748 patients (47.2%) had psychiatric disorders, including 408 (25.7%) with schizophrenia and 470 (29.7%) with neurologic disease. With regard to treatment, 408 patients (25.7%) were admitted to the ICU, 193 (12.2%) had tracheal intubation and 70 (4.4%) had hemodialysis. Only 17 patients received electroconvulsive therapy. Dantrolene was administered to 768 patients (49.0%) and bromocriptine to 176 patients (11.1%).

Table 1 shows the descriptive statistics and in-hospital mortality of the neuroleptic malignant syndrome patients. In-hospital mortality was 8.6%. A linear trend was seen between age and mortality. The proportion of patients aged 49 years or younger was larger in teaching hospitals (38.5%) than in nonteaching hospitals (25.1%). Cardiovascular disease was associated with increased neuroleptic malignant syndrome–related mortality (20.8%).

Propensity Score Analysis

Of the 1,585 neuroleptic malignant syndrome patients, data on antipsychotic prescribing were obtained from 638 patients, including 423 with prescriptions for typical antipsychotics and 215 with prescriptions for atypical antipsychotics. By 1-to-1 matching, 210 pairs of typical and atypical antipsychotic users were selected. The C statistic for goodness of fit was 0.571. Table 2 shows the characteristics of both groups; no significant difference in patient background was shown between the groups except ICU admission (31.4% in typical antipsychotics group and 21.0% in atypical antipsychotics group; $P = .020$).

In-hospital mortality was 7.6% (n/n = 16/210) in typical antipsychotic users and 3.3% (n/n = 7/210) in atypical antipsychotic users. Although the typical antipsychotic group showed higher mortality, Fisher exact test showed no statistical significance ($P = .084$). Table 3 shows the results of logistic regression analysis for in-hospital mortality. Hospital type was not a significant factor after adjustment for age, and none of the patient characteristics were significantly associated with

Table 1. In-Hospital Mortality in Each Subgroup (N = 1,585)

Variable	n	In-Hospital Death n	In-Hospital Death %	*P*
Total		136	8.6	
Type of hospital				
Teaching	384	20	5.2	.007
Nonteaching	1,201	116	9.7	
Sex				
Male	912	83	9.1	.389
Female	673	53	7.9	
Age, y				
≤ 29	105	5	4.8	.003
30–49	344	24	7.0	
50–69	588	44	7.5	
≥ 70	548	63	11.5	
Comorbidities				
Malignancy	31	3	9.7	.826
Diabetes mellitus	103	11	10.7	.431
Cardiovascular disease	106	22	20.8	< .001
Cerebrovascular disease	59	7	11.9	.359
Chronic lung diseases	22	1	4.5	.496
Liver cirrhosis	14	2	14.3	.444
Chronic renal failure	14	2	14.3	.444
Therapeutic procedures				
ICU admission	408	49	12.0	.004
Hemodialysis	70	12	17.1	.009
Intubation	193	71	36.8	< .001
Dantrolene	768	93	12.1	< .001
Bromocriptine	176	17	9.7	.588
ECT	17	0	0.0	.204

Abbreviations: ECT = electroconvulsive therapy, ICU = intensive care unit.

in-hospital mortality. Atypical antipsychotics users were less likely to have in-hospital death compared with typical antipsychotic users, but the difference was not significant (OR = 0.44; 95% CI, 0.17–1.11; *P* = .084).

DISCUSSION

The mortality of neuroleptic malignant syndrome has not been well documented.[1,11] In the present study, we identified 1,585 neuroleptic malignant syndrome inpatients and compared the mortality of the syndrome caused by atypical antipsychotics with mortality caused by typical antipsychotics in a large sample of 210 propensity-matched pairs. Descriptive statistics of all 1,585 neuroleptic malignant syndrome patients showed that neuroleptic malignant syndrome–related mortality was 8.6% in this study, which was similar to that in a 2007 US report (10%).[1] Despite widespread awareness and earlier diagnosis of this disorder, neuroleptic malignant syndrome remains a significant source of mortality among patients receiving antipsychotics. Men were dominant with regard to number of patients in our study, which was consistent with a previous report.[2] The association between age and neuroleptic malignant syndrome occurrence remains unclear. Neuroleptic malignant syndrome occurrence has been reported in all ages, in parallel with antipsychotic use.[12] Several reports have indicated that neuroleptic malignant syndrome was rare in teenagers[6,13] and was frequently seen in patients in their 30s and 40s,[14,15] while our study showed a predominance in older generations aged 50 or older. Our study also showed that 105 cases (6.6%) were aged 29 or younger. Clinicians should pay attention to the possibility of neuroleptic malignant syndrome

Table 2. Comparison of Characteristics After Propensity Score Matching (n = 420)

Characteristic	Typical Antipsychotics (n = 210) n	Typical Antipsychotics (n = 210) %	Atypical Antipsychotics (n = 210) n	Atypical Antipsychotics (n = 210) %	*P*
Hospital type (teaching)	56	26.7	65	31.0	.389
Sex (male)	121	57.6	124	59.0	.843
Age, y					
≤ 49	50	23.8	65	31.0	.756
50–69	83	39.5	78	37.1	
≥ 70	67	31.9	67	31.9	
Comorbidities					
Malignancy	4	1.9	4	1.9	> .99
Diabetes mellitus	9	4.3	9	4.3	> .99
Cardiovascular disease	12	5.7	13	6.2	> .99
Cerebrovascular disease	6	2.9	9	4.3	.447
Chronic lung diseases	3	1.4	2	1.0	> .99
Liver cirrhosis	3	1.4	2	1.0	> .99
Chronic renal failure	4	1.9	2	1.0	.685
Therapeutic procedures					
ICU admission	66	31.4	44	21.0	.020
Hemodialysis	9	4.3	13	6.2	.512
Intubation	26	12.4	15	7.1	.099
Dantrolene	108	51.4	95	45.2	.241
Bromocriptine	29	13.8	25	11.9	.662
ECT	5	2.4	8	3.8	.575

Abbreviations: ECT = electroconvulsive therapy, ICU = intensive care unit.

Table 3. Logistic Regression Analysis for In-Hospital Mortality (n = 420)

Variable	OR	95% CI	*P*
Type of hospital			
Nonteaching	1.00		
Teaching	0.92	0.35–2.47	.872
Sex			
Male	1.00		
Female	1.53	0.65–3.61	.328
Age, y			
≤ 49	1.00		
50–69	1.51	0.49–4.72	.475
≥ 70	1.54	0.45–5.25	.491
Cardiovascular disease	2.36	0.60–9.36	.222
ICU admission	1.50	0.59–3.84	.400
Antipsychotic			
Typical	1.00		
Atypical	0.44	0.17–1.11	.084

Abbreviation: ICU = intensive care unit.

in all treated age groups. The findings that 133 of 193 patients who underwent intubation required ICU admission while 44 of 70 patients who received hemodialysis required ICU admission indicate that ICU admission was correlated with intubation or hemodialysis. Thus, we selected only ICU admission as a proxy measure of clinical severity of neuroleptic malignant syndrome and added it to the independent variables in the logistic regression model.

Generally, physicians take a patient's medical condition into consideration when selecting an antipsychotic drug. For example, olanzapine and quetiapine are not used for patients with diabetes mellitus because the drugs potentially increase the blood glucose level and patients may develop diabetic ketoacidosis.[16–19] Because the patients were not randomly assigned to receive each type of antipsychotic, the application of propensity score matching in our study was useful for adjusting patient backgrounds and controlling for the

physician's propensity to select drugs. The mortality following atypical antipsychotic–induced neuroleptic malignant syndrome was 3.3% in our study, which was similar to that reported in a previous literature review.[4] The mortality was substantially lower in the atypical antipsychotics group compared with the typical antipsychotics group (7.6%), but the difference was not significant. Despite a relatively large sample size, the present study was unable to identify between-group differences in mortality because of the low incidence of neuroleptic malignant syndrome. Further studies based on even larger samples are required. Fisher exact test showed that our sample size offered statistical power of 0.418. To obtain significant differences in mortality between the groups, the necessary sample size was calculated to be 756 pairs (statistical power = 0.7), 936 pairs (statistical power = 0.8), or 1,222 pairs (statistical power = 0.9). At the same time, a pathophysiological investigation of neuroleptic malignant syndrome caused by atypical antipsychotics should be performed. The tendency of a lower mortality rate of neuroleptic malignant syndrome in atypical antipsychotic users may reflect differences in the pathophysiology and clinical severity between the groups. Several previous reports advocated a new notion of "atypical neuroleptic malignant syndrome."[5,7] According to the reports, *atypical neuroleptic malignant syndrome* can be defined as neuroleptic malignant syndrome induced by atypical antipsychotics and having atypical clinical manifestations and qualitative and quantitative differences in pathophysiology compared with typical neuroleptic malignant syndrome. Our results may lend support to the establishment of this disease concept.

Several limitations should be acknowledged. First, recorded diagnoses in an administrative claims database are less well validated than those in planned prospective studies. However, several advantages of the data submission processes in the DPC database, such as *ICD*-based diagnoses and physician-dependent reporting, increase the accuracy and consistency of reporting.[20] Second, our propensity-matched analysis was based only on cases whose use of antipsychotics was reported. Third, other drugs were not investigated because of their lower possibility of inducing neuroleptic malignant syndrome.

CONCLUSION

This study was the first investigation comparing neuroleptic malignant syndrome–related mortality between typical and atypical antipsychotic users based on data from a large-scale database. Mortality of neuroleptic malignant syndrome in patients treated with atypical antipsychotics was less than half that in patients treated with typical antipsychotics, but the difference was not significant. To clarify the difference in neuroleptic malignant syndrome–related mortality between typical and atypical antipsychotic users, further studies with larger samples are needed. However, the possibility of lower mortality in neuroleptic malignant syndrome caused by atypical antipsychotics could be explained by differences in pathophysiology and clinical severity.

Drug names: aripiprazole (Abilify), bromocriptine (Parlodel, Cycloset, and others), clozapine (Clozaril, FazaClo, and others), dantrolene (Dantrium and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).

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Author contributions: Drs Yasunaga, Horiguchi, and Matsuda conducted data collection, data synthesis, and data management. Dr Nakamura constructed the study design, conducted data analysis, and wrote the draft manuscript. All authors approved the final version.

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