population-based, but focused on mortality among psychiatric outpatients.[4] Few cohort studies have thus been performed in which the severities of both somatic and psychiatric diseases are equivalent to the level of admission required.

The purpose of this cross-sectional study in Tokyo was to clarify whether psychiatric beds in general hospitals play sufficient roles in medical comorbidities of psychiatric patients or not. Such epidemiological data in Tokyo, where there are approximately 12 million inhabitants, might contribute to public policy not only in Japan but also in other countries.

METHODS

1. Design

This was a cross-sectional study performed all over Tokyo during the 2-month period from April 1 to May 31 2007.

In general, when medical or surgical diseases occur in patients with severe psychiatric symptoms, patients are treated in psychiatric beds in general hospitals. However, it is difficult to arrange such medical care for psychiatric emergency patients during the night and holidays, or for inpatients of psychiatric hospitals.

In Tokyo, the medical comorbidity service for inpatients of psychiatric hospitals is provided by the Tokyo Metropolitan Government. Five hospitals (204 beds) are responsible for this system (P-GHP). Moreover, the psychiatric emergency service provided by the Tokyo Metropolitan Government practically covers medical or surgical diseases occurring in psychiatric emergency patients during the night and holidays. Three hospitals (12 beds) are responsible for this system (N-GHP). Other situations, i.e. during the daytime on weekdays, patients who require admission due to both somatic and psychiatric diseases are ordinarily admitted to a psychiatric ward in one of 28 general hospitals (1135 beds, D-GHP). There were no beds overlapping with each other in these three systems. The total number of patients who require admission due to both somatic and psychiatric diseases in these three systems means the total number of those in Tokyo.

Twenty-one of 28 D-GHP, which correspond to 75.2% of psychiatric beds of all the 28 D-GHP, participated in the study. Moreover, all of the three N-GHP (100%) and all of the five P-GHP (100%) participated in the study.

The study protocol was approved by the institutional review board of Juntendo University School of Medicine. The approved protocol did not require informed consent from patients because the data in this observational study remained anonymous and were analyzed in the aggregate.

2. Data collection

The subjects of this study were patients who required admission due to both somatic and psychiatric diseases. Psychiatric patients comorbid with somatic diseases, patients with somatic diseases who had recently contracted psychiatric diseases, and patients whose acute psychiatric symptoms were caused by somatic diseases, were all included, although patients who did not require admission were not included. Data collection was consecutive.

The information collected included the following: (i) demographic characteristics such as age and gender; (ii) medical or surgical diagnoses; (iii) psychiatric discharge diagnoses according to ICD-10; (iv) the level of emergency, e.g. need to be admitted within the day of request, within 2 days, within a week, or no need for haste; (v) the duration of waiting for admission; (vi) kinds of facilities where patients are introduced; (vii) suicidal behavior; (viii) restraint or seclusion; (ix) the Excited Component for the Positive and Negative Syndrome Scale (PANSS-EC: Excitement, Hostility, Tension, Uncooperativeness, Poor impulse control) and Lack of Judgment and Insight;[5,6] and (x) the length of hospital-stay for the somatic diseases.

At the same time, we surveyed cases that could not be admitted to psychiatric beds in general hospitals despite the existence of somatic diseases requiring admission. The information collected includes the following: (i) demographic characteristics such as age and gender; (ii) suspected medical or surgical diagnoses; (iii) suspected psychiatric diagnoses according to ICD-10; (iv) suicidal behavior; and (v) the reason that the patient could not be admitted.

3. Analyses

Differences between categorical variables were calculated using Fisher's exact test. Differences between sequential variables were calculated using the Student's *t*-test. The statistical test was two-tailed. A *P*-value of less than 0.05 was regarded as statistically significant.

RESULTS

1. Demographic and clinical characteristics of patients who were admitted to psychiatric beds in general hospitals due to both somatic and psychiatric diseases requiring admission

The number of patients who were admitted to D-GHP during the study period was 997. Of the 997 patients, 174 patients (17.5%) were due to both somatic and psychiatric diseases. The number of patients who were admitted to N-GHP during the study period was 242. Of the 242 patients, 10 patients (4.1%) had accompanying somatic diseases requiring admission. The number of patients who were admitted to P-GHP due to both somatic and psychiatric diseases during the study period was 142. Accordingly, the total number of patients who were admitted to psychiatric beds in general hospitals due to both somatic and psychiatric diseases during the study period was 326 (Table 1). The mean age of the 326 patients was 61.7 years (SD 16.2, Table 1). Forty-eight percent of these patients were 65 years or older and 46% were male.

Medical or surgical diagnoses of the 326 patients at discharge are shown in Table 2. Of these, 194 patients (60%) were medical, and the remaining 132 patients (40%) were surgical. Respiratory diseases were the most frequent (19%), followed by diseases requiring orthopedic surgery (13%), diseases requiring abdominal surgery (10%), and gastrointestinal and hepatic diseases (10%). Detailed descriptions of frequent somatic diseases were in the following order: pneumonia (14%), femoral neck fracture (6%), diabetes mellitus (4%), cerebral infarction (3%), and colon cancer (3%).

Psychiatric diagnoses (ICD-10) of the 326 patients at discharge were distributed as follows (Table 1): organic, including symptomatic, mental disorders (F0), 28%; mental and behavioral disorders due to psychoactive substance use (F1), 7%; schizophrenia, schizotypal, and delusional disorders (F2), 40%; mood disorders (F3), 15%; neurotic, stress-related and somatoform disorders (F4), 2%; behavioral syndromes associated with physiological disturbances and physical factors (F5), 1%; disorders of adult personality and behavior (F6), 2%; mental retardation (F7), 4%; epilepsy (G40), 1%. Detailed descriptions of the category F0 were as follows: dementia and organic amnesic syndrome (F00-F04), 18%; delirium and others (F05-F07), 10%.

Discrepancy between the level of emergency and the duration of waiting for admission was as follows. The total number of patients who need to be admitted immediately due to severe somatic diseases was 88. Of these, 30 patients could not be admitted within the day (34%). Similarly, the total number of patients who needed to be admitted within 2 days of request due to the severity of somatic disease was 66. Of these, 14 patients could not be admitted within 2 days (21%). The total number of patients who need to be admitted within a week of request due to the severity of somatic diseases was 84. Of these, 20 patients could not be admitted within a week (24%).

Among the 326 patients, 42 patients (13%) were associated with suicide. Thirty-two patients (10%) had attempted suicide (Table 1), and 10 patients (3%) had had obvious suicidal ideation.

Physical restraints were used in 114 patients (35%) among the 326 patients, and seclusion rooms were used in eight patients (3%).

Table 1. Characteristics of psychiatric patients with medical comorbidities who were admitted to psychiatric beds in general hospitals and of those who could not be admitted

Group	*n*	Age*** (year)	Gender (%, men)	Diagnosis (%)			Suicidal attempt*** (%)	Diseases requiring surgery** (%)
				F0	F2	F3		
Admitted	326	61.7 [16.2]	46	28	40	15	10	40
Not admitted	88	48.0 [20.2]	48	22	41	16	35	58

Data are presented as percentage except age (mean [SD]). Diagnoses were made with ICD-10. $^{**}P < 0.001$, $^{***}P < 0.0001$. Admitted, psychiatric patients with medical comorbidities who were admitted to psychiatric beds in general hospitals; F0, organic, including symptomatic, mental disorders; F2, schizophrenia, schizotypal and delusional disorders; F3, mood disorders; Not admitted, psychiatric patients with medical comorbidities who could not be admitted to psychiatric beds in general hospitals.

Table 2. The list of medical and surgical diseases of psychiatric patients who were admitted to psychiatric beds in general hospitals

Disease	*n* (%)	Detailed descriptions (*n*)
Medical		
Respiratory	61 (19%)	Pneumonia (44), Pulmonary tuberculosis (4), Pneumothorax (3) Acute exacerbation of chronic respiratory failure (3) Acute interstitial pneumonia (2), Others (5)
Gastrointestinal and hepatic	32 (10%)	Ileus (9), Hematemesis and melena (7), Liver cirrhosis (3) Alcoholic liver disease (2), Acute pancreatitis (2), Others (9)
Neurological	25 (8%)	Cerebral infarction (11), Parkinson's disease (3), Herpes encephalitis (2) Status epileptics (2), Others (7)
Endocrinological	22 (7%)	Diabetes mellitus (14), Others (8)
Nephrological	16 (5%)	Acute renal failure (7), Chronic renal failure (2), Others (7)
Hematological	15 (5%)	Anemia (5), Malignant lymphoma (3), Others (7)
Cardiological	10 (3%)	Acute heart failure or acute exacerbation of chronic heart failure (6) Others (4)
Collagen disease	3 (1%)	Systemic Lupus erythematodes (1), Others (2)
Infectious disease	3 (1%)	HIV (2), Neurosyphilus (1)
Others	7 (2%)	
Surgical		
Orthopedic	42 (13%)	Femoral neck fracture (19), Pelvic fracture (5), Vertebral fracture (4) Finger tendon injury (3), Other fractures (9), Others (2)
Abdominal	32 (10%)	Colon cancer (10), Gastric cancer (5), Acute cholecystitis (5) Liver cancer (2), Abdominal stab wound (2) Perforation of gastrointestinal tract (2), Others (6)
Gynecological	15 (5%)	Breast cancer (8), Cesarean section (3) Carcinoma of the uterine cervix (2), Ovarian cancer (2)
Neurosurgery	14 (4%)	Subdural hematoma (7), Brain contusion (3), Brain tumor (3) Others (1)
Chest	10 (3%)	Lung cancer (8), Others (2)
Dermatological	7 (2%)	Pressure ulcer (2), Others (5)
Urological	6 (2%)	Bladder cancer (1), Prostatic cancer (1), Others (4)
Ophthalmological	5 (2%)	Cataract (4), Other (1)
Oral surgery	1 (0%)	Osteomyelitis (1)
Total		326

The median scores of PANSS-EC and Lack of Judgment and Insight in the 326 patients were 13 (range 5–35) and 4 (range 1–7), respectively.

The median length of hospital-stay was 28 days.

2. Demographic and clinical characteristics of patients who could not be admitted to psychiatric beds in general hospitals despite the existence of both somatic and psychiatric diseases requiring admission

The number of patients who could not be admitted to D-GHP despite the existence of both somatic and psychiatric diseases requiring admission during the study period was 88 (Table 1). The rate of rejection of admission to D-GHP despite the existence of both somatic and psychiatric diseases requiring admission was 34%. Meanwhile, there were no patients who could not be admitted to the N-GHP or P-GHP. The mean age of the 88 patients was 48.0 years (SD 20.2, Table 1). Twenty-nine percent of these patients were 65 years or older and 48% were male.

Medical or surgical diagnoses of the 88 patients are shown in Table 3. Of these, 37 patients (42%) were medical, and the remaining 51 patients (58%) were surgical. Remarkably, the rate of surgical diseases in

Table 3. The list of medical and surgical diseases of psychiatric patients who could not be admitted to psychiatric beds in general hospitals

Disease	*n* (%)	Detailed descriptions (*n*)
Medical		
Gastrointestinal and hepatic	7 (8%)	Ileus (2), Hematemesis and melena (2), Hepatic encephalopathy (2) Others (1)
Neurological	5 (6%)	Encephalitis (3), Consciousness disturbance (2)
Nephrological	5 (6%)	Chronic renal failure (3), Malignant syndrome (2)
Cardiological	5 (6%)	Acute heart failure or acute exacerbation of chronic heart failure (5)
Others	15 (17%)	
Surgical		
Orthopedic	19 (22%)	Multiple fractures (6), Femoral neck fracture (4), Other fractures (9)
Abdominal	19 (22%)	Abdominal stab wound (3), Inguinal hernia (3), Colon cancer (3) Esophageal cancer (2), Acute cholecystitis (2), Acute appendicitis (2) Others (4)
Gynecological	6 (7%)	Cesarean section (3), Ovarian cancer (2), Other (1)
Neurosurgery	3 (3%)	Head injury (2), Other (1)
Chest	2 (2%)	Lung cancer (2)
Dermatological	2 (2%)	Pressure ulcer (2)
Total	88	

patients who could not be admitted to psychiatric beds in general hospitals was higher than that in patients who were admitted (Relative Risk = 0.70, $P = 0.0038$, Table 1). Diseases requiring orthopedic surgery (22%) and abdominal surgery (22%) were the most frequent, followed by gastrointestinal and hepatic diseases (8%), and gynecological diseases (7%). Detailed descriptions of frequent somatic diseases were in the following order: multiple fractures (7%), acute heart failure (6%), and femoral neck fracture (5%).

Psychiatric diagnoses (ICD-10) of the 88 patients were distributed as follows: F0, 22%; F1, 3%; F2, 41%; F3, 16%; F4, 10%; F6, 6%; and F7, 2%. Detail descriptions of the category F0 were as follows: F00-F04, 3%; F05-F09, 18%.

Among the 88 patients, 33 patients (38%) were associated with suicide. Thirty-one patients (35%) had attempted suicide, and two patients (2%) had had obvious suicidal ideation. Remarkably, the rate of having attempted suicide in patients who could not be admitted to psychiatric beds in general hospitals was higher than that in patients who were admitted (Relative Risk = 0.28, $P < 0.0001$, Table 1).

The reasons for refusal of admission despite the existence of both somatic and psychiatric diseases requiring admission were as follows: 'psychiatric beds were full', 68%; 'impossible to manage such a patient because of an open ward', 7%; 'no specialist corresponding to the somatic disease', 5%; 'impossible to perform an operation without delay', 3%; 'others', 17%.

DISCUSSION

1. Characteristics of patients who require admission to psychiatric beds in general hospitals due to both somatic and psychiatric diseases

The mean age of 61.7 years (SD 16.2) in the 326 patients who were admitted to psychiatric beds in general hospitals due to both somatic and psychiatric diseases may reflect the increase of the aged population. Unfortunately, there have been no similar reports with population-based design, so it is impossible to compare this result with others.

In the present study, the most frequent medical and surgical diseases were pneumonia and femoral neck fracture, respectively. To our knowledge, this appears to be a new finding with respect to the needs for admission to psychiatric beds in general hospitals.

So far, a wide range of comorbidity has been described, with chronic medical illnesses such as hypertension, heart disease, pulmonary disease, and diabetes.[7,8] However, patients with such comorbidity do not necessarily require admission because of the inclusion of chronic state. Meanwhile, in a mortality survey, heart diseases and suicide have been reported as the leading causes of death.[3] However, patients under such imminent conditions may be brought in not to a general hospital psychiatric unit but to a cardiac care unit or a critical care center. Therefore, the survey of mortality cannot estimate the needs for psychiatric beds in general hospitals. Thus, there are obvious differences in kinds of diseases between reports focusing on comorbidity and those focusing on mortality, both of which do not seem to reflect the needs for admission to psychiatric beds in general hospitals.

With respect to psychiatric diagnoses, schizophrenia and associate disorders (ICD-10: F2) was most frequent as previously reported.[3] The second highest frequency was organic mental disorders (F1). In particular, the high frequency of dementia (F00-F04) was remarkable, indicating the increased aged population.

Although the median score of PANSS-EC was not so high, that of Lack of Judgment and Insight was moderate. Lack of judgment and insight may have disturbed the treatment of somatic diseases, which may explain the high frequency of physical restraints.

The reason for the finding of a significantly higher mean age of patients who could be admitted compared with patients who could not be admitted is unclear. In general, the average age of patients admitted to psychiatric hospitals is high. In the present study, 142 patients were admitted to P-GHP (to which patients from psychiatric hospitals were admitted), while there was no patient who could not be admitted to P-GHP. Inclusion of such aged population in the group of patients who could be admitted may have caused this difference in age.

2. Do psychiatric beds in general hospitals function in quality?

It is remarkable that the rate of having attempted suicide in patients who could not be admitted to psychiatric beds in general hospitals was higher than that in patients who were admitted (Table 1). The finding suggests that psychiatric beds in general hospitals did not necessarily accept psychopathologically severe cases with medical comorbidities. The findings that the median score of PANSS-EC was not so high, and that the median score of Lack of Judgment and Insight was moderate, may support this.

It is also remarkable that the rate of surgical diseases in patients who could not be admitted to psychiatric beds in general hospitals was higher than that in patients who were admitted (Table 1). The finding suggests that psychiatric beds in general hospitals did not necessarily accept medically severe cases with psychiatric diseases.

Furthermore, it is serious that 34% of patients who needed to be admitted immediately due to severe somatic diseases could not be admitted within the day. The finding suggests that psychiatric beds in general hospitals did not necessarily accept emergency cases with medical comorbidities.

Thus, psychiatric beds in general hospitals do not necessarily function for medical comorbidities in psychiatric patients, especially in severe and emergency cases.

3. Do psychiatric beds in general hospitals function in quantity?

The incidence of medical comorbidity for which psychiatric patients should be hospitalized appears to be at least 25 per 100 000 inhabitants in Tokyo, as described elsewhere.[9] As there are approximately 12 million inhabitants in Tokyo, 3000 patients may require admission to psychiatric beds in general hospitals due to both somatic and psychiatric diseases. As the median length of hospital-stay was 28 days, the number of patients who can utilize one bed is calculated on 13.0 per year. As the estimated number of patients is 3000 per year in Tokyo, the number of beds needed is calculated as 231.

Unexpectedly, this number is much smaller than the total number of psychiatric beds in general hospitals in Tokyo (1135 beds). However, the rate of rejection of admission to D-GHP despite the existence of both somatic and psychiatric diseases requiring admission was not low (34%). An explanation is that the major roles of psychiatric beds in general hospitals include not only medical comorbidities but also electroconvulsive therapy, differential diagnosis using neuroimaging methods, and emergency cases with abnormal physiological conditions.[10] Therefore, it is not conclusive that the total number of psychiatric beds in general hospitals in Tokyo may be enough for medical comorbidities.

In order to provide a medical care service for psychiatric patients efficiently, research concerning the roles of psychiatric units in general hospitals, i.e. not only medical comorbidities but also other functions mentioned above, will be needed. Thereafter, the priority among various roles of psychiatric units in general hospitals will be determined, which will lead to the provision of an efficient medical care service for psychiatric patients.

The strength and weaknesses of this study bear discussion. The strength of our study is that it included all psychiatric patients who lived in a defined area during the study period. One limitation is that our finding may represent only a metropolis. Therefore, a similar study in provincial areas is needed. Another limitation is that our findings may represent only the mental health system in Japan. However, such findings may have significance for comparison of differences in mental health systems among countries. Such a population-based study should be conducted regularly in order to improve the treatment of somatic diseases in psychiatric patients and to clarify the function of a general hospital psychiatric unit.

ACKNOWLEDGMENTS

The authors thank Dr Hirotsugu Kikumoto, Dr Ichiro Masudomi, Mr Ichiro Yoshida, and Ms Yukiko Masuda (Tokyo Metropolitan Government), Dr Kunitoshi Hato (Japanese Association of Mental Health Services), Dr Kunihiro Isse and Dr Mitsuru Nakamura (Tokyo Metropolitan Toshima General Hospital), Dr Takao Nishimura and Dr Hikaru Furuta (Tokyo Metropolitan Fuchu General Hospital), Dr Hiroshi Suwa (Tokyo Metropolitan Ebara General Hospital), Dr Mitsuo Suyama (Tokyo Metropolitan Bokuto General Hospital), Dr Hiroshi Umezu (Tokyo Metropolitan Matsuzawa Hospital), Dr Yoshihiro Yahiro (Tama Saisei Hospital), Dr Naohiro Fujimura (Tokyo Musashino Hospital), Dr Hiroshi Mitsushio (Ohme-City General Hospital), Dr Hirokatsu Kono (Kyosai Tachikawa General Hospital), Dr Masahiro Shintani (Tokyo Metropolitan Hiroo General Hospital), Dr Takashi Takeuchi (Tokyo Medical and Dental University Hospital), Dr Joichiro Shirahase (Keio University Hospital), Dr Ken Inada (Tokyo Women's University Hospital), Dr Amane Tateno (Nippon Medical School Hospital), Dr Shuichi Katsuragawa (Toho University Omori Medical Center), Dr Tsuyoshi Akiyama (Kanto Medical Center NTT EC), Dr Hiroki Kocha (National Hospital Organization Tokyo Medical Center), Dr Tomomichi Kameyama (Tokyo Teishin Hospital), Dr Jin Habu (JSDF Central Hospital), Dr Yukako Seki and Dr Kobun Imai (International Medical Center of Japan), Dr Kazunori Nakajima (Sanraku Hospital), Dr Takeo Muraki (JR Tokyo General Hospital), Dr Yosuke Ichimiya, Dr Yoichiro Matsubara, and Dr Ryo Kumagai (Juntendo Tokyo Koto Geriatric Medical Center), for collecting the data.

This work was supported by a grant from the Ministry of Health, Welfare, and Labor of the Japanese Government (Research on Psychiatric and Neurological Diseases and Mental Health, H19-009).

REFERENCES

1 Kobayashi T. A study on medical comorbidities in psychiatric patients in a provincial area. **In**: Kurosawa H (ed.). *A Report on Psychiatric Emergency, Including Medical Comorbidities and Dementia* (Research on Psychiatric and Neurological Diseases and Mental Health, H19-009). Japanese Government Publication 2008; 97–126 (in Japanese).
2 Lyketsos CG, Dunn G, Kaminsky MJ, Breakey WR. Medical comorbidity in psychiatric inpatients: Relation to clinical outcomes and hospital length of stay. *Psychosomatics* 2002; **43**: 24–30.
3 Miller B, Paschall CB III, Svendsen DP. Mortality and medical comorbidity among patients with serious mental illness. *Psychiatr. Serv.* 2006; **57**: 1482–1487.
4 Meloni D, Miccinesi G, Bencini A *et al.* Mortality among discharged psychiatric patients in Florence, Italy. *Psychiatr. Serv.* 2006; **57**: 1474–1481.
5 Key SR, Opler LA, Fiszbein A. *Positive and Negative Syndrome Scale (PANSS) Rating Manual.* Multi-Health System Inc., Toronto, 1991.
6 Breier A, Meehan K, Birkett M *et al.* A double-blind, placebo-controlled dose–response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Arch. Gen. Psychiatry* 2002; **59**: 441–448.
7 Felker B, Yazel JJ, Short D. Mortality and medical comorbidity among psychiatric patients: A review. *Psychiatr. Serv.* 1996; **47**: 1356–1363.
8 Goldman LS. Comorbid medical illness in psychiatric patients. *Curr. Psychiatry Rep.* 2000; **2**: 256–263.
9 Hatta K, Kurosawa H, Arai H. Hospitalization for medical comorbidities among psychiatric patients in Tokyo. *Psychiatr. Serv.* 2007; **58**: 1502.
10 Hatta K, Takahashi T, Nakamura H *et al.* Abnormal physiological conditions in acute schizophrenic patients on emergency admission: Dehydration, hypokalemia, leukocytosis and elevated serum muscle enzymes. *Eur. Arch. Psychiatry Clin. Neurosci.* 1998; **248**: 180–188.

Schizophrenia Research 113 (2009) 49–55

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Effectiveness of second-generation antipsychotics with acute-phase schizophrenia

Kotaro Hatta [a,*], Koji Sato [b], Hiroshi Hamakawa [c], Hiroshi Takebayashi [d], Naoto Kimura [e], Shinichiro Ochi [e], Yasuhiko Sudo [f], Nozomu Asukai [g], Hiroyuki Nakamura [h], Chie Usui [a], Toshitaka Kawabata [i], Toyoaki Hirata [j], Yutaka Sawa [c]

[a] *Department of Psychiatry, Juntendo University School of Medicine, Tokyo, Japan*
[b] *Gunma Psychiatric Medical Center, Isezaki, Japan*
[c] *Sawa Hospital, Osaka, Japan*
[d] *Saitama Prefectural Psychiatric Hospital, Ina-machi, Japan*
[e] *Matsuyama Memorial Hospital, Matsuyama, Japan*
[f] *Tosa Hospital, Kochi, Japan*
[g] *Tokyo Institute of Psychiatry, Tokyo, Japan*
[h] *Department of Environmental and Preventive Medicine, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan*
[i] *Kyoto Prefecture Rakunan Hospital, Kyoto, Japan*
[j] *Shizuoka Psychiatric Medical Center, Shizuoka, Japan*

Schizophrenia Research 113 (2009) 49–55

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Effectiveness of second-generation antipsychotics with acute-phase schizophrenia

Kotaro Hatta [a,*], Koji Sato [b], Hiroshi Hamakawa [c], Hiroshi Takebayashi [d], Naoto Kimura [e], Shinichiro Ochi [e], Yasuhiko Sudo [f], Nozomu Asukai [g], Hiroyuki Nakamura [h], Chie Usui [a], Toshitaka Kawabata [i], Toyoaki Hirata [j], Yutaka Sawa [c]

[a] Department of Psychiatry, Juntendo University School of Medicine, Tokyo, Japan
[b] Gunma Psychiatric Medical Center, Isezaki, Japan
[c] Sawa Hospital, Osaka, Japan
[d] Saitama Prefectural Psychiatric Hospital, Ina-machi, Japan
[e] Matsuyama Memorial Hospital, Matsuyama, Japan
[f] Tosa Hospital, Kochi, Japan
[g] Tokyo Institute of Psychiatry, Tokyo, Japan
[h] Department of Environmental and Preventive Medicine, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan
[i] Kyoto Prefecture Rakunan Hospital, Kyoto, Japan
[j] Shizuoka Psychiatric Medical Center, Shizuoka, Japan

ARTICLE INFO

Article history:
Received 14 March 2009
Received in revised form 28 May 2009
Accepted 29 May 2009
Available online 24 June 2009

Keywords:
Olanzapine
Risperidone
Quetiapine
Aripiprazole
Emergency
Clinical trial

ABSTRACT

Purpose: Although olanzapine may have advantages over other second-generation antipsychotics (SGAs) regarding longer time to treatment discontinuation among chronically ill patients, little evidence has been provided for the comparative effectiveness of SGAs in the acute phase. We aimed to determine if any of four SGAs were more effective in treating newly admitted acute schizophrenic patients. We performed a rater-blinded, randomized controlled trial of four SGAs in 15 psychiatric emergency sites. Eligible patients were 18–64 years old and met diagnostic criteria for schizophrenia, acute schizophrenia-like psychotic disorder, or schizoaffective disorder. A final total of 78 patients were randomly assigned by means of sealed envelopes to receive risperidone (3–12 mg/day; $n=20$), olanzapine (10–20 mg/day; $n=17$), quetiapine (300–750 mg/day; $n=20$), or aripiprazole (12–30 mg/day; $n=21$), with follow-up at 8 weeks. The primary outcome measure was all-cause treatment discontinuation.

Results: Overall, 37% (29/78) of patients discontinued the study medication before 8 weeks: 25% for risperidone; 12% for olanzapine; 55% for quetiapine; and 52% for aripiprazole. Time to treatment discontinuation for any cause was significantly longer in the olanzapine group than in the quetiapine ($p=0.006$) or aripiprazole ($p=0.008$) groups, but not compared to the risperidone group ($p=0.32$). Time to treatment discontinuation was significantly longer in the risperidone group than in the quetiapine group ($p=0.048$), but not compared to the aripiprazole group ($p=0.062$). However, the rate of p.r.n. intramuscular haloperidol use was significantly higher in the aripiprazole group than in other groups ($p=0.029$).

Conclusion: Olanzapine and risperidone are superior to quetiapine and aripiprazole for the acute treatment of psychosis in hospitalized patients.

1. Introduction

A meta-analysis of comparisons of second-generation antipsychotics (SGAs) in the treatment of schizophrenia has

* Corresponding author. Department of Psychiatry, Juntendo University School of Medicine, Hongo 2-1-1, Bunkyo-ku, Tokyo 113-8421, Japan. Tel./fax: +81 3 5802 1071.
E-mail address: khatta@juntendo.ac.jp (K. Hatta).

0920-9964/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2009.05.030

shown that olanzapine is superior to aripiprazole, quetiapine, risperidone, and ziprasidone, and that risperidone offers greater efficacy than quetiapine and ziprasidone (Leucht et al., 2009). As such analyses are based on synthesized data regardless of focus on acute phase or chronic phase, and regardless of inpatients or outpatients, such outcomes are not necessarily realized in actual clinical practice, particularly in emergency and acute phase situations. In chronically ill or first-episode patients, olanzapine may offer advantages over other second-generation antipsychotics regarding longer time to treatment discontinuation and better drug adherence (Johnsen and Jørgensen, 2008; Kahn et al., 2008; Lieberman et al., 2005). Meanwhile, little evidence is available regarding the comparative effectiveness of second-generation antipsychotics in the acute phase. In particular, studies are rarely performed with emergency-based newly admitted patients. Optimal methods to treat such patients in the acute phase of psychosis remain a big concern in clinical practice, as the length of hospital-stay mainly depends on that. Kraus et al. (2005) reported risperidone and olanzapine as equally efficacious based on a lack of significant differences in mean duration of hospitalization between groups randomly assigned to either drug. In another randomized clinical trial (RCT), McCue et al. (2006) reported haloperidol, olanzapine, and risperidone as significantly more effective than aripiprazole, quetiapine, and ziprasidone based on improvements in mental status to the point where the patient no longer required acute inpatient care. However, follow-up period was not defined in the former study, and was only 3 weeks in the latter study. In addition, outcome measures were duration of hospitalization in the former study and no longer needing acute inpatient care in the latter, which might have reflected idiosyncrasies of clinical practice by the psychiatric inpatient service at those facilities. To the best of our knowledge, no other RCTs have focused on acute phase with newly admitted schizophrenic patients but without support from pharmaceutical companies.

We aimed to determine if any of four SGAs, namely risperidone, olanzapine, quetiapine, and aripiprazole, were more effective in treating newly admitted acute-phase schizophrenia patients of Asian ethnicity, without support from pharmaceutical companies, using a generalizable measure.

2. Methods

2.1. Setting and participants

Of the 28 psychiatric emergency wards registered by Japanese government, 15 participated (54%). These were located in all over Japan, and were responsible for local emergency cases. Between July 1 and August 31, 2008, a total of 813 patients were assessed for eligibility. Eligible patients were 18–64 years old, newly admitted as emergency cases, and met criteria of the ICD-10 for schizophrenia, acute schizophrenia-like psychotic disorder, or schizoaffective disorder. Patients with obvious complications such as liver dysfunction, renal dysfunction, heart failure, respiratory failure, or diabetes mellitus were excluded. Patients who were pregnant or who wanted to become pregnant were likewise excluded.

2.2. Study design

All study protocols were approved by the institutional review board at each site, and written informed consent was obtained from patients or their legally authorized representatives. Patients who refused oral medication were treated with injections at first. After resolution of agitation, the investigators informed patients orally and in writing about the trial, and invited them to participate.

Patients were randomly assigned by means of sealed envelopes to receive risperidone, olanzapine, quetiapine, or aripiprazole. Initial doses of risperidone, olanzapine, quetiapine, and aripiprazole were 3 mg/day, 10 mg/day, 300 mg/day, and 12 mg/day, respectively, considering dose equivalency (Kane et al., 2003). These doses were not low, as patients were all newly admitted as emergency cases. Doses were increased or decreased at the discretion of the treating psychiatrist. Maximum dose of each study drug was within the upper limit, i.e., 12 mg/day for risperidone, 20 mg/day for olanzapine, 750 mg/day for quetiapine, or 30 mg/day for aripiprazole as mentioned in the package insert texts. Use of benzodiazepines was allowed and documented. However, use of mood stabilizers and antidepressants was not permitted. Use of anticholinergic drugs was also not allowed unless acute extrapyramidal side effects appeared.

2.3. Procedures

Before the start of the trial, site-coordinators were trained to assess outcomes as raters. A training video was used to train raters in the assessment of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1991). The primary outcome measure was all-cause discontinuation. The assigned drug was discontinued when the treating psychiatrist judged the efficacy of the drug to be insufficient, when the treating psychiatrist judged side-effects of the drug to be intolerable, or when the patient reported non-adherence. Before the judgment of insufficient efficacy, dose of the drug was increased to the maximum. When the status of patient was unchanged or worse according to Clinical Global Impression Change rating scale (CGI-C) as a score ≥ 5 (Guy, 1976) despite the maximum dose, the treating psychiatrist judged the efficacy of the drug to be insufficient, and discontinued the assigned drug. Reasons for discontinuation of the assigned drug were recorded.

Efficacy outcomes consisted of PANSS, CGI, and Global Assessment of Functioning (GAF) (Jones et al., 1995). Safety and tolerability outcomes were determined based on vital signs, weight, laboratory data, electrocardiography (ECG), and the Drug-induced Extrapyramidal Symptom Scale (DIEPSS), which includes parkinsonism, akathisia, dystonia, and dyskinesia (Inada, 1996). Data including PANSS, CGI, GAF, vital signs, weight, laboratory data, ECG, and DIEPSS were collected at the time of admission and every 2 weeks thereafter. Data were also collected at the time of discontinuation of the assigned drug. Sexual side effects were recorded when reported by patients, and sedation was recorded when described by patients as an aversive subjective experience or when observed. Raters were not involved with treatment, and were blinded to drug assignments.

2.4. Statistical analysis

Kraus et al. (2005) reported that 80% of newly admitted acutely ill psychotic patients assigned to olanzapine or risperidone remained on the study medication at discharge. McCue et al. (2006) reported that approximately 90% of newly admitted acute schizophrenia patients assigned to olanzapine or risperidone and approximately 60% of those assigned to aripiprazole or quetiapine achieved effective treatment. Accordingly, the assumption of the discontinuation rate could have been 10–20% for risperidone and olanzapine and 40% for quetiapine and aripiprazole. However, we assumed higher discontinuation rates, as clinical settings were psychiatric emergency wards registered by Japanese government and were responsible for local severe emergency cases.

We assumed treatment discontinuation rates at 8-week follow-up of 30% in patients receiving risperidone, 40% in patients receiving olanzapine, 60% in patients receiving quetiapine, and 60% in patients receiving aripiprazole. The statistical power was set as power $= 1-\beta = 80\%$, and sensitivity to $\alpha = 5\%$ to be able to detect differences in the effects of drugs. Power analysis consequently set the required number of patients at 15 patients per group.

Kaplan–Meier curves were used to estimate the probability of treatment discontinuation at 8 weeks. Differences between categorical variables in patient demographics and clinical characteristics were calculated using the χ^2 test. When χ^2 calculations were not valid, Fisher's exact test combining two or more rows or columns was used. Differences between sequential variables were calculated using one-way analysis of variance (ANOVA). If data were not sampled from Gaussian distributions, a non-parametric test (Kruskal–Wallis test) was used. Statistical analyses were performed using SPSS version 16.0 J software (SPSS, Tokyo, Japan). All statistical tests were two-tailed. Values of $p<0.05$ were regarded as statistically significant.

3. Results

Fig. 1 shows the trial profile. Eighty patients were randomly assigned to four treatment groups (Fig. 1). The rate of study participation among eligible patients was 24% (80/334). One patient assigned to risperidone and another assigned to aripiprazole withdrew consent, and thus were not included in the final analysis. Baseline characteristics of randomized patients were much the same between groups (Table 1). Table 2 shows outcomes. Mean (±SD) doses of risperidone,

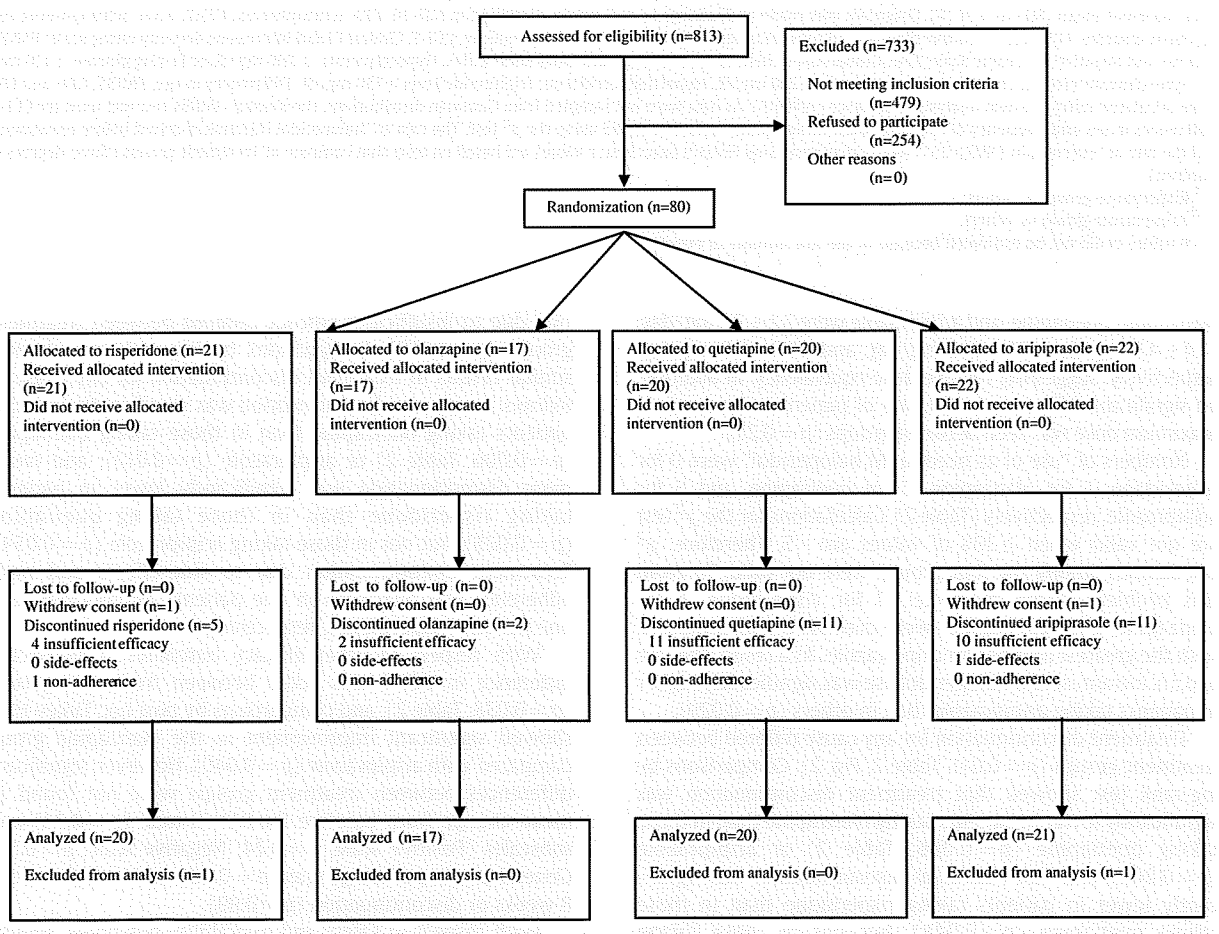

Fig. 1. Trial profile.

Table 1
Baseline characteristics of patients.

	Risperidone ($n=20$)	Olanzapine ($n=17$)	Quetiapine ($n=20$)	Aripiprazole ($n=21$)	p
Age (years)	41.1 (8.8)	39.8 (10.8)	39.8 (11.2)	42.1 (12.4)	0.88
Men	9/20 (45%)	12/17 (71%)	4/20 (20%)	8/21 (38%)	0.34
Asian	20/20 (100%)	17/17 (100%)	20/20 (100%)	21/21 (100%)	
Diagnosis					
F20	17/20 (85%)	17/17 (100%)	20/20 (100%)	21/21 (100%)	
F23.2	1/20 (5%)	0/17 (0%)	0/20 (0%)	0/21 (0%)	
F25	2/20 (10%)	0/17 (0%)	0/20 (0%)	0/21 (0%)	
Substance dependence[c]					
	2/20 (10%)	0/17 (0%)	1/20 (5%)	0/21 (0%)	
Antipsychotic-naïve	7/20 (35%)	7/17 (41%)	8/20 (40%)	8/21 (38%)	0.98
The same antipsychotic assigned and received[c]					
	4/20 (20%)	2/17 (12%)	0/20 (0%)	1/21 (5%)	
Haloperidol injection received before enrolment[a]					
	2/20 (10%)	6/17 (35%)	6/20 (30%)	4/21 (19%)	0.13
CGI-S	5.5 (0.9)	5.1 (0.8)	5.1 (0.8)	5.0 (1.0)	0.29
PANSS					
Total	93.6 (18.0)	104.3 (21.4)	100.4 (22.6)	88.5 (20.7)	0.094
Positive scale	26.7 (5.7)	28.5 (8.4)	26.5 (5.5)	25.1 (8.3)	0.54
Negative scale	20.1 (9.3)	25.3 (10.2)	25.1 (9.1)	19.5 (6.2)	0.067
General psychopathology scale					
	46.8 (10.8)	50.5 (10.3)	48.8 (12.6)	43.9 (11.7)	0.32
GAF	25.6 (7.3)	28.2 (6.0)	28.7 (8.7)	27.2 (10.7)	0.67
BMI (kg/m^2)	23.8 (4.7)	23.9 (4.0)	22.0 (4.8)	21.9 (3.4)	0.28
Overweight (BMI≥25)[b]	7/20 (35%)	7/17 (41%)	3/20 (15%)	3/21 (14%)	0.24
Hyperglycemia	0/20 (0%)	0/17 (0%)	0/20 (0%)	0/21 (0%)	
Hypercholesterolemia [c]	1/20 (5%)	0/17 (0%)	0/20 (0%)	1/21 (5%)	
Hypertriglyceridemia [c]	2/20 (10%)	2/17 (12%)	0/20 (0%)	1/21 (5%)	

Data represent mean (SD) or n/N (%). Diagnosis was made at discharge or at 8 weeks according to ICD-10. F20, schizophrenia; F23.2, acute schizophrenia-like psychotic disorder; F25, schizoaffective disorder. All substance dependence was alcohol dependence. CGI-S, Clinical Global Impression Severity rating scale; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; BMI, body mass index. Hyperglycemia: ≥200 mg/dL or fasting glucose ≥126 mg/dL. Hypercholesterolemia: cholesterol concentration ≥220 mg/dL. Hypertriglyceridemia: triglyceride level ≥150 mg/dL. Differences in age, PANSS, GAF, and BMI were calculated using one-way analysis of variance (ANOVA). As data were not sampled from Gaussian distributions, the Kruskal–Wallis test was used for CGI-S. Differences in sex and frequency of "antipsychotic-naïve" status were calculated using the χ^2 test. The rate of "haloperidol injection received before enrolment" and the rate of "overweight (BMI≥25)" were calculated using Fisher's exact test. p values are based on tests that compare all treatment groups (three degrees of freedom).

[a] Risperidone-group vs. others.
[b] Aripiprazole-group vs. others.
[c] p values could not be estimated because of the low number of events.

olanzapine, quetiapine, and aripiprazole were 7.2±3.1 mg/day, 17.4±4.7 mg/day, 579±210 mg/day, and 23.6±6.5 mg/day, respectively, suggesting relative dose equivalency. In addition, no significant difference in the rate of patients who received maximum dose was seen between groups ($p=0.22$).

Numbers of "use of as needed IM haloperidol" were 0 for risperidone, 1 for olanzapine, 2 for quetiapine, and 5 for aripiprazole, respectively (Table 2). Calculations for the χ^2 test are not valid when ≥20% of values are <5. Therefore, χ^2 calculations among the four groups were not valid. To avoid this problem, three rows—i.e., 0 for risperidone, 1 for olanzapine, 2 for quetiapine—were combined and compared with the greatest number for aripiprazole. As a result, the rate of p.r.n. intramuscular haloperidol use was significantly higher in patients taking aripiprazole than in others ($p=0.029$).

Treatment discontinuation for any cause differed between treatment groups ($p=0.011$, Table 2, Fig. 2). Comparisons by log-rank test showed that treatment discontinuation was significantly lower in patients taking olanzapine than in those taking quetiapine ($p=0.006$, Table 2) or aripiprazole ($p=0.008$), and that treatment discontinuation was significantly lower in patients taking risperidone than in those taking quetiapine ($p=0.048$), but not in those taking aripiprazole ($p=0.062$). In addition, treatment discontinuation due to insufficient efficacy differed between treatment groups ($p=0.010$). Comparisons by log-rank test showed similar results in treatment discontinuation for any cause as follows: treatment discontinuation was significantly lower in patients taking olanzapine than in those taking quetiapine ($p=0.006$, Table 2) or aripiprazole ($p=0.013$); and treatment discontinuation was significantly lower in patients taking risperidone than in those taking quetiapine ($p=0.025$), but not in those taking aripiprazole ($p=0.054$). Treatment discontinuation due to side-effects and non-adherence was only seen in one patient (aripiprazole) and one patient (risperidone), respectively.

With respect to other efficacy outcomes, a significant difference in CGI-C was noted between treatment groups ($p=0.038$, Table 2), and comparisons by post hoc Tukey HSD showed significant improvement in the olanzapine group compared with aripiprazole ($p=0.040$). However, significant differences between treatment groups were not found in mean change from baseline for PANSS total ($p=0.34$) and subscales (Positive scale, $p=0.24$; Negative scale, $p=0.54$; General psychopathology scale, $p=0.40$), and in GAF score at 8 weeks or discontinuation ($p=0.99$).

With respect to safety and tolerability outcomes, significant differences between treatment groups were not found in

Table 2
Outcomes of treatment discontinuation, efficacy, and safety and tolerability.

	Risperidone ($n=20$)	Olanzapine ($n=17$)	Quetiapine ($n=20$)	Aripiprazole ($n=21$)	p
Mean dose (mg/day [SD])	7.2 (3.1)	17.4 (4.7)	579 (210)	23.6 (6.5)	
Maximum dose received	9/20 (45%)	13/17 (76%)	11/20 (55%)	10/21 (48%)	0.22
Use of as needed IM haloperidol[a]	0/20 (0%)	1/17 (6%)	2/20 (10%)	5/21 (24%)	0.029
Adjunctive BZ[b]	19/20 (95%)	12/17 (71%)	9/20 (45%)	20/21 (95%)	0.0003
Anticholinergic drug [c]	7/20 (35%)	2/17 (12%)	2/20 (10%)	3/21 (14%)	0.039
Discontinuation for any cause[d]	5/20 (25%)	2/17 (12%)	11/20 (55%)	11/21 (52%)	0.011
Comparisons by log-rank test (p)					
Risperidone		0.32	0.048	0.062	
Olanzapine			0.006	0.008	
Quetiapine				0.98	
Discontinuation because of insufficient efficacy[d]	4/20 (20%)	2/17 (12%)	11/20 (55%)	10/21 (48%)	0.010
Comparisons by log-rank test (p)					
Risperidone		0.49	0.025	0.054	
Olanzapine			0.006	0.013	
Quetiapine				0.80	
Discontinuation because of side-effects	0/20 (0%)	0/17 (0%)	0/20 (0%)	1/21 (5%)	
Discontinuation because of non-adherence	1/20 (5%)	0/17 (0%)	0/20 (0%)	0/21 (0%)	
CGI-C	3.4 (1.7)	2.8 (1.1)	4.1 (2.1)	4.4 (2.1)	0.038
Comparisons by post hoc Tukey HSD					
Risperidone		0.72	0.62	0.32	
Olanzapine			0.13	0.040	
Quetiapine				0.96	
PANSS (mean change from baseline)					
Total	−24.7 (27.9)	−33.4 (20.8)	−28.9 (28.6)	−18.4 (26.0)	0.34
Positive scale	−10.8 (10.9)	−12.6 (9.3)	−9.4 (8.6)	−6.5 (9.1)	0.24
Negative scale	−3.3 (5.6)	−5.6 (5.7)	−6.3 (9.5)	−3.8 (5.2)	0.54
General psychopathology scale	−10.7 (14.7)	−15.1 (10.8)	−13.3 (13.3)	−8.1 (14.1)	0.40
GAF	48.1 (19.4)	48.7 (14.7)	46.6 (21.5)	47.8 (21.7)	0.99
Any serious adverse event	0/20 (0%)	0/17 (0%)	0/20 (0%)	0/21 (0%)	
Extrapyramidal symptoms (DIEPSS)					
Any symptoms	13/20 (65%)	8/17 (47%)	5/20 (25%)	8/21 (38%)	0.076
Parkinsonism	12/20 (60%)	5/17 (29%)	5/20 (25%)	7/21 (33%)	0.098
Akathisia[c]	5/20 (25%)	2/17 (12%)	2/20 (10%)	4/21 (19%)	0.30
Dystonia[e]	3/20 (15%)	1/17 (6%)	0/20 (0%)	0/21 (0%)	
Dyskinesia[e]	1/20 (5%)	0/17 (0%)	1/20 (5%)	0/21 (0%)	
Weight change from baseline (kg)	−0.8 (2.5)	1.1 (3.8)	1.2 (3.2)	−0.5 (2.8)	0.098
Fasting glucose change from baseline (mg/dL)	1.2 (15.7)	−3.2 (11.3)	−5.2 (14.6)	4.2 (13.1)	0.17
Cholesterol change from baseline (mg/dL)	1.9 (52.0)	8.5 (36.3)	8.6 (30.1)	0.4 (36.5)	0.88
Triglycerides change from baseline (mg/dL)	20.4 (55.4)	16.7 (82.7)	4.0 (64.6)	−3.3 (50.8)	0.62

Data represent mean (SD) or n/N (%), unless otherwise indicated. IM, intramuscular injection; BZ, benzodiazepine; CGI-C, Clinical Global Impression Change rating scale; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; DIEPSS, Drug-induced Extrapyramidal Symptom Scale. p values are based on tests that compare all treatment groups (three degrees of freedom).

[a] Aripiprazole-group vs. others.
[b] Quetiapine-group vs. others.
[c] Risperidone-group vs. others.
[d] Percentages represent Kaplan–Meier estimates of treatment discontinuation within 8 weeks.
[e] p values could not be estimated due to the low number of events.

extrapyramidal symptoms ($p=0.076$, Table 2) such as parkinsonism ($p=0.098$), akathisia ($p=0.30$), dystonia, or dyskinesia. However, the rate of patients who required anticholinergic drugs was greater in the risperidone group than in other groups ($p=0.039$). No significant differences between treatment groups were identified in mean change from baseline for weight ($p=0.098$), fasting glucose ($p=0.17$), cholesterol ($p=0.88$), or triglycerides ($p=0.62$). Sexual side effects and sedation were not observed.

4. Discussion

Our study has shown that in newly admitted acute schizophrenic patients, treatment discontinuation over

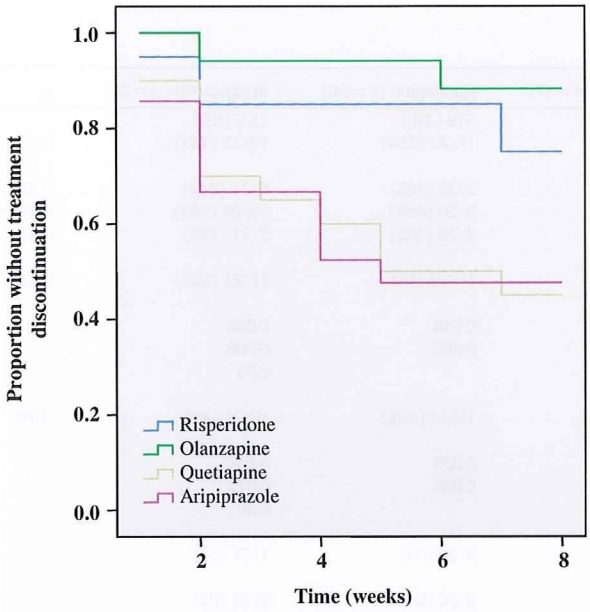

Fig. 2. Time to treatment discontinuation for any cause. Kaplan–Meier estimates of weeks to discontinuation (95% CI) were 7.0 (6.0–7.9) for risperidone, 7.5 (6.8–8+) for olanzapine, 5.3 (4.1–6.5) for quetiapine, and 5.1 (3.9–6.4) for aripiprazole, respectively. For olanzapine, no upper limit for the CI could be estimated, as the upper limit was above the maximum follow-up time.

8 weeks was significantly greater in patients assigned to quetiapine or aripiprazole than in those assigned to olanzapine, and was significantly greater in patients assigned to quetiapine than in those assigned to risperidone. Meanwhile, the difference between risperidone and aripiprazole groups was not quite significant. However, the rate of patients who required p.r.n. intramuscular haloperidol was significantly higher in the aripiprazole group than in other groups, whereas no patients in the risperidone group required p.r.n. intramuscular haloperidol. Without p.r.n. intramuscular haloperidol, treatment discontinuation in patients assigned to aripiprazole would have increased, although that in patients assigned to risperidone would not have been affected. These results were caused not by differences in side-effects or non-adherence, but by differences in insufficient efficacy (Table 2). With respect to treatment discontinuation, olanzapine and risperidone were thus superior to quetiapine and aripiprazole for newly admitted acute schizophrenic patients. Although symptomatic improvement measured by PANSS and global improvement measured by GAF did not differ significantly between groups, global improvement as measured with CGI-C partially supports this. Power analysis set the required number of patients at 15 patients per group to detect differences not in CGI-C scores, but in treatment discontinuation rate. More patients may thus have been needed to detect significant differences in CGI-C scores.

Two previous RCTs have focused on acute phase with newly admitted schizophrenic patients, without support from pharmaceutical companies (Kraus et al., 2005; McCue et al., 2006), although methodological limitations were present, as mentioned in the Introduction. The present findings were derived from outcome measures more clearly defined than those in previous RCTs, and are consistent with findings in those RCTs. From another perspective, no discrepancy was seen between the present findings with Asian ethnicity and previous findings from mainly white and African-American ethnicity.

The review by Leucht et al. (2009) concluded that, in tailoring drug treatment to the individual patient, small efficacy superiorities must be weighed against large differences in side effects and cost. However, meta-analyses are based on synthesized data regardless of focus on acute phase or chronic phase, and regardless of inpatient or outpatient status. Outcomes of meta-analyses are thus not necessarily applicable to real clinical practice, particularly under emergency and acute-phase situations. In the present results, more than half of the patients assigned to quetiapine or aripiprazole could not bear monotherapy with the assigned drug, while only 12% and 25% of patients assigned to olanzapine and risperidone, respectively, could not bear monotherapy. These differences may be clinically significant for emergency and acute-phase situations.

As no significant differences were seen in the appearance of extrapyramidal symptoms between groups, extrapyramidal symptoms did not appear to affect treatment discontinuation during the acute phase period, as mentioned above. Likewise, as no significant differences were noted between treatment groups in mean change from baseline for weight, fasting glucose, cholesterol, or triglycerides, metabolic side-effects did not appear to affect treatment discontinuation during the acute-phase period. McCue et al. (2006) have also shown a lack of significant differences in parkinsonian side-effects, akathisia, and spontaneous reports of adverse events, whereas Kraus et al. (2005) reported neither formal evaluations of extrapyramidal symptoms nor accurate assessment for metabolic side-effects. Sexual side effects and sedation also did not appear to affect treatment discontinuation. To detect these accurately, however, systematic assessment may be needed. As this study was performed on emergency situations, the priority of safety and tolerability assessments was on life-threatening conditions.

This effectiveness study suggests that olanzapine and risperidone are superior to quetiapine and aripiprazole for the acute treatment of newly admitted schizophrenic patients. One strength of our study was that all participants were psychiatric emergency cases requiring admission, mirroring real clinical practice. Furthermore, outcome measures were clearly defined compared with previous studies focusing on acute phase treatment. Absence of support from pharmaceutical companies and a focus exclusively on patients of Asian ethnicity were also characteristics of the study. One limitation was that sample size was relatively small, although the number of participants was above the required number as set by power analysis. Since obtaining informed consent in emergency situations is not easy, the rate of participation in the study among eligible patients was 24%. This rate is not particularly low for emergency situations. Another limitation was the single-blind design. Both clinicians and patients may have had expectations about individual SGAs in terms of therapeutic potency in an acute psychotic episode, dosage requirements, side-effect profile, and likely need for p.r.n. medication. Such expectations could influence the dosage prescribed, decisions to prescribe p.r.n. medication, and decisions to discontinue the assigned drug. However, obtaining informed consent for a double-blind study of emergency

situations may be extremely difficult, so the rate of participation in a double-blind study among eligible patients could well be much lower than that in a single-blind study such as this. As excessively low participation rates cannot reflect real practice, this issue is of particular concern for research into emergency situations. More studies performed in real clinical practice with minimal bias are required to assist clinicians in making rational treatment decisions.

Role of the funding source

This work was supported by a grant from the Ministry of Health, Welfare, and Labor of the Japanese Government (Research on Psychiatric and Neurological Diseases and Mental Health, H19-009). The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, and the decision to submit the paper for publication.

Contributors

Kotaro Hatta, Nozomu Asukai, Toshitaka Kawabata, Toyoaki Hirata, Yutaka Sawa, Koji Sato, Hiroshi Hamakawa, Hiroshi Takebayashi, Naoto Kimura, Shinichiro Ochi, and Yasuhiko Sudo designed the study. Kotaro Hatta obtained funding and supervised the study. Kotaro Hatta, Hiroyuki Nakamura, and Chie Usui analyzed the data. Kotaro Hatta and Hiroyuki Nakamura interpreted the data and drafted the report. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgements

The authors thank Dr. Haruo Watanabe, Dr. Yasuyuki Deguchi, Dr. Homaro Yamamoto, Dr. Tomohiro Suto, Dr. Takeshi Tanaka, Dr. Toshiaki Hiraoka, Dr. Taro Otachi, Dr. Tomoyuki Maehara, Dr. Keisuke Takahashi, Dr. Tatsuro Ono, Dr. Ryo Saito, Dr. Aya Matsuoka, Dr. Mitsuru Takei, Dr. Morihiro Shimabukuro, Dr. Hajime Sugiyama, Dr. Akihito Sakanaka, Dr. Yoshitaka Miyama, Dr. Takanobu Okuno, Dr. Takeshi Katsu, Dr. Akira Okae, Dr. Juichiro Naoe, Dr. Kazuki Tabata, Dr. Fumiyoshi Morikawa, Dr. Tomokazu Kidani, Dr. Minoru Takeshima, Dr. Koichi Kurata, Dr. Naoki Hayashi, Dr. Toru Wakejima, Dr. Mika Teranishi, Dr. Masatake Kurita, Dr. Asaho Hasegawa, Dr. Taketomo Minoshima, Dr. Shinichi Sato, Dr. Shuken Sai, Dr. Yutaka Shirai, Dr. Satoshi Okazaki, Dr. Keitaro Sueda, Dr. Chikako Hashimoto, Dr. Mitsuru Nakamura, Dr. Kunihiro Isse, Dr. Hidekazu Masaki, and Takao Nishimura, for the collection of data.

References

Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology. US Dept of Health, Education, and Welfare, Bethesda.

Inada, T., 1996. Evaluation and Diagnosis of Drug-induced Extrapyramidal Symptoms: Commentary on the DIEPSS and Guide to its Usage. Seiwa Shoten Publishers, Tokyo.

Johnsen, E., Jørgensen, H.A., 2008. Effectiveness of second generation antipsychotics: a systematic review of randomized trials. BMC Psychiatry 8, 31. doi:10.1186/1471-244X-8-31.

Jones, S.H., Thornicroft, G., Coffey, M., Dunn, G., 1995. A brief mental health outcome scale-reliability and validity of the Global Assessment of Functioning (GAF). Br. J. Psychiatry 166 (5), 654–659.

Kahn, R.S., Fleischhacker, W.W., Boter, H., Davidson, M., Vergouwe, Y., Keet, I.P., Gheorghe, M.D., Rybakowski, J.K., Galderisi, S., Libiger, J., Hummer, M., Dollfus, S., López-Ibor, J.J., Hranov, L.G., Gaebel, W., Peuskens, J., Lindefors, N., Riecher-Rössler, A., Grobbee, D.E., EUFEST study group, 2008. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet 371 (9618), 1085–1097.

Kane, J.M., Leucht, S., Carpenter, D., Docherty, J.P., 2003. Optimizing pharmacologic treatment of psychotic disorders. J. Clin. Psychiatry 64 (suppl 12), 1–100.

Kay, S.R., Opler, L.A., Fiszbein, A., 1991. Positive and Negative Syndrome Scale (PANSS) Rating Manual. Multi-Health System Inc., Toronto.

Kraus, J.E., Sheitman, B.B., Cook, A., Reviere, R., Lieberman, J.A., 2005. Olanzapine versus risperidone in newly admitted acutely ill psychotic patients. J. Clin. Psychiatry 66 (12), 1564–1568.

Leucht, S., Komossa, K., Rummel-Kluge, C., Corves, C., Hunger, H., Schmid, F., Asenjo Lobos, C., Schwarz, S., Davis, J.M., 2009. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am. J. Psychiatry 166 (2), 152–163.

Lieberman, J.A., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Keefe, R.S., Davis, S.M., Davis, C.E., Lebowitz, B.D., Severe, J., Hsiao, J.K., Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators, 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N. Engl. J. Med. 353 (12), 1209–1223.

McCue, R.E., Waheed, R., Urcuyo, L., Orendain, G., Joseph, M.D., Charles, R., Hasan, S.M., 2006. Comparative effectiveness of second-generation antipsychotics and haloperidol in acute schizophrenia. Br. J. Psychiatry 189 (11), 433–440.

Psychiatry and Clinical Neurosciences 2009; 63: 658–662 doi:10.1111/j.1440-1819.2009.02010.x

Regular Article

Prevalence of i.v. thiopental use in psychiatric emergency settings in Japan

Kotaro Hatta, MD,PhD,[1]* Mitsuru Nakamura, MD,[2] Kenichi Yoshida, MD,[3] Hiroshi Hamakawa, MD,PhD,[4] Toru Wakejima, MD,[5] Takao Nishimura, MD,[6] Toshitaka Kawabata, MD,[7] Toyoaki Hirata, MD,[8] Chie Usui, MD,PhD[1] and Yutaka Sawa, MD,PhD[4]

[1]*Department of Psychiatry, Juntendo University School of Medicine,* [2]*Department of Psychiatry, Tokyo Metropolitan Toshima General Hospital, Tokyo,* [3]*Department of Psychiatry, Chiba Psychiatric Medical Center, Chiba,* [4]*Department of Psychiatry, Sawa Hospital, Osaka,* [5]*Department of Psychiatry, Tokyo Metropolitan Matsuzawa Hospital,* [6]*Department of Psychiatry, Tokyo Metropolitan Fuchu General Hospital, Tokyo,* [7]*Department of Psychiatry, Kyoto Prefecture Rakunan Hospital, Kyoto and* [8]*Department of Psychiatry, Shizuoka Psychiatric Medical Center, Shizuoka, Japan*

Aim: Because i.v. barbiturates such as thiopental carry the risk of apnea and laryngeal spasm in asthmatic patients, reducing the use of barbiturate in emergency situations is important. The purpose of the present study was therefore to investigate the prevalence of i.v. thiopental as a choice of sedation in behavioral emergency settings, we conducted a cross-sectional multicenter study.

Methods: Psychiatric emergency departments of seven hospitals were studied during a 4-month period. Patients with a score >15 on the Excited Component of the Positive and Negative Syndrome Scale (PANSS-EC) who received i.v. medication were included in the study. Drugs were chosen according to the Japanese guidelines, in which the first injection was either haloperidol or benzodiazepine in accordance with clinical requirements. A second injection, which was the opposite drug to the first injection was administered as needed. Only when excitement obviously increased following the first injection, which was considered uncontrollable without thiopental according to expert experience, was thiopental given as a second injection. A total of 137 patients were included. The mean age was 40.4 years (SD 13.1), and the rate of male gender, drug-naïve, and F2 (schizophrenia, schizotypal and delusional disorders) on the ICD-10 were 48.9%, 29.9%, and 65.7%, respectively.

Results: The rate of patients treated with thiopental as a second injection was 8.0% ($n = 11$). All of the first injections in patients treated with thiopental were not haloperidol but benzodiazepines ($P = 0.0072$).

Conclusion: Because this multicenter study has an epidemiological character, the prevalence of i.v. thiopental use in psychiatric emergency settings in Japan is considered to be 8.0%.

Key words: agitation, benzodiazepine, disinhibition, haloperidol, sedation.

INTRAVENOUS BARBITURATE SUCH as thiopental is a frequently used agent for induction of general anesthesia, along with propofol. In particular, barbiturate anesthetics are recommended for refractory generalized convulsive status epileptics.[1,2] But high frequency of apnea,[3] and high frequency of wheezing[4] have lowered the recommendation level of anesthetic management in asthma.[5]

In addition to its function as an agent for induction of general anesthesia, i.v. barbiturate has played a role as a sedating agent. According to the Japanese guidelines for psychiatric emergency treatment,

Correspondence: Kotaro Hatta, MD, PhD, Department of Psychiatry, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. Email: khatta@juntendo.ac.jp.
Received 25 April 2008; revised 28 May 2009; accepted 29 May 2009.

version 2003, barbiturate is listed as a second-line recommendation for patients who require i.v. medication.[6] In an emergency situation, however, it is not necessarily known in advance whether a patient has asthma or not. Furthermore, barbiturate does not have an antagonist. Therefore, it is important to reduce the use of barbiturate in emergency situations.

In order to investigate the prevalence of i.v. thiopental as a choice of sedation in behavioral emergency settings, we conducted a cross-sectional multicenter study. In particular, the difference in the prevalence of thiopental use following benzodiazepine injection and following haloperidol injection was focused on.

METHODS

Subjects

This cross-sectional study was carried out over a 4-month period (May–August 2007) in seven psychiatric emergency departments. These emergency departments serve catchment areas of a total of 21420 000 people, which is one-sixth of the Japanese population. In each area, psychiatric emergency patients requiring hospitalization are hospitalized under the responsibility of the hospital. Most of the patients included in the present study were involved in behavioral emergencies and approximately 60% of them were brought in by the police. All were involuntary admissions, being an immediate danger to themselves or others, according to the 1995 Law Concerning Mental Health and Welfare for the Mentally Disabled.

During the study period, 1612 patients visited or were brought in to the seven psychiatric emergency departments. Of these, 372 patients scored ≥15 on the Excited Component of the Positive and Negative Syndrome Scale (PANSS-EC). Among these, 267 patients refused oral medication. Three patients were medicated i.m., and the remaining 264 patients received i.v. medication. Because written informed consent could not be obtained from 127 of these patients or their legally authorized representatives, a total of 137 patients (52%) were included in the study.

The mean age of 137 patients was 40.4 ± 13.1 years, and the number of men was 67 (48.9%). The number of drug-naïve patients was 41 (29.9%).

Procedure

All study protocols were approved by the institutional review board at each site, and written informed consent was obtained from patients or their legally authorized representatives. Patients who refused oral medication were medicated via the i.m. or i.v. routes. I.m. medication was chosen when there was little possibility of complication of somatic disease or abnormal physiological conditions. I.v. medication was chosen when uncooperative patients were required to receive computed tomography (CT), magnetic resonance imaging (MRI), or lumbar puncture, or when uncooperative patients were required to receive fluid therapy due to dehydration, hypokalemia, or elevation of serum muscle enzymes such as creatine phosphokinase (CPK).[7] Patients who received i.v. medication, and who recorded a score ≥15 on the PANSS-EC (Excitement; Hostility; Tension; Uncooperativeness; Poor impulse control)[8,9] when visiting or being brought to the psychiatric emergency department services, were included in this study.

Drugs were chosen according to the Japanese guidelines for rapid tranquilization, in which benzodiazepine and haloperidol are listed as i.v. medication.[6] Some investigators may have chosen haloperidol as being superior to benzodiazepine as a first injection, and another may have chosen the opposite. Because the present study was naturalistic, the choice of a first injection between benzodiazepine and haloperidol was at the investigators' discretion. If sufficient sedation was achieved with the first injection, a second injection was not given. Although dosage was at the investigators' discretion, it was arranged that the investigators would use the minimum dose for patient safety. A second injection, which was a cross-over between benzodiazepine and haloperidol, was administered 5–10 min after the first injection if the first injection did not achieve sufficient sedation for brain CT or MRI. Only when excitement obviously increased following the first injection, which was considered uncontrollable without thiopental from expert experience, was thiopental allowed as a second injection. Anticholinergic medications were not permitted unless acute extrapyramidal side-effects appear.

Screening evaluation included medical history, physical examination, measurement of vital signs and laboratory tests. Diagnoses were made according to ICD-10 criteria.

Treatment efficacy was measured in terms of psychopathology, which was assessed using PANSS-EC and Clinical Global Impression (CGI).[10] PANSS-EC was assessed at baseline and every 15 min over the course of 1 h. Patients were observed to determine whether they were awake or asleep 15 min after the first injection. CGI Severity rating scale (CGI-S) was assessed at baseline, and CGI Change rating scale (CGI-C) was assessed at 60 min after medication. The raters were trained in outcome parameters.

To assess safety, the blood pressure, heart rate, and hemoglobin oxygen saturation (SpO_2) were measured at baseline and every 15 min thereafter, over the course of 1 h. Moreover, SpO_2 and electrocardiogram (ECG) were continuously monitored to detect airway obstruction and ventricular tachyarrhythmia in all patients given i.v. medication, this being standard practice in Japan.[11] For extrapyramidal symptoms, including akathisia, parkinsonian signs and dyskinetic movements, the Drug-induced Extrapyramidal Symptom Scale was utilized.[12] The most severe scores recorded at any time during the 12 h post-therapy period were reported.

Among all the subjects, the mean baseline PANSS-EC score was 21.2 ± 7.3, and the mean baseline CGI-S score was 5.2 ± 1.2. The number of F2 (schizophrenia, schizotypal and delusional disorders) diagnoses was 90 (65.7%).

Statistical analysis

Differences between categorical variables in patient demographics were calculated using Fisher's exact test. Differences between sequential variables in patient demographics and clinical characteristics were calculated using Student's *t*-test (with the Welch *t*-test when appropriate). If the data were not sampled from Gaussian distributions, a non-parametric test (Mann–Whitney *U*-test) was used. All statistical tests were two-tailed. $P < 0.05$ was regarded as statistically significant.

RESULTS

As a first injection, 50 patients received haloperidol, and 87 patients received benzodiazepine (flunitrazepam for 82 patients and diazepam for five patients). The choice between flunitrazepam and diazepam depended on doctor preference. The mean dose of haloperidol as a first injection was 9.1 ± 2.9 mg. Among them, nine patients did not require a second injection. The mean dose of flunitrazepam and diazepam was 3.6 ± 2.5 mg and 22.0 ± 14.8 mg, respectively. Among patients who received flunitrazepam as a first injection, 46 patients did not require a second injection. Among patients who received diazepam as a first injection, three patients did not require a second injection.

The rate of patients treated with thiopental as a second injection was 8.0% ($n = 11$) among 137 patients who received i.v. medication. As shown in Table 1, there were no statistically significant differences in age, gender, the rate of drug-naïve patients, mean baseline PANSS-EC score, mean baseline CGI-S score, and the distribution of diagnosis between patients treated with and without i.v. thiopental as a

Table 1. Patients treated with and without i.v. thiopental as a second injection

Characteristics	With thiopental ($n = 11$)	Without thiopental ($n = 126$)	*P*
Age (years), mean ± SD	33.9 ± 8.8	41.0 ± 13.3	0.088
Gender, % men (*n*)	27.3 (3)	50.8 (64)	0.21
Drug-naive, % (*n*)	18.2 (2)	31.0 (39)	0.51
Baseline PANSS-EC (mean ± SD)	20.6 ± 5.1	21.4 ± 7.2	0.72
Baseline CGI-S (mean ± SD)	4.5 ± 1.9	5.3 ± 1.1	0.17
F2 in diagnosis, % (*n*)	72.7 (8)	65.1 (82)	0.75
First injection			
Haloperidol, % (*n*)	0 (0)	39.7 (50)	
Benzodiazepine, % (*n*)	100 (11)	60.3 (76)	0.0072

$P < 0.05$ was regarded as statistically significant. Diagnoses were made according to ICD-10 at discharge. Benzodiazepines include flunitrazepam (82 patients) and diazepam (five patients).
CGI-S, Clinical Global Impressions Severity rating scale (1–7); F2, schizophrenia, schizotypal and delusional disorders; PANSS-EC, Excited Component for the Positive and Negative syndrome scale (5–35).

second injection. All of the first injections in patients treated with thiopental, however, were not haloperidol but benzodiazepines ($P = 0.0072$). The mean dose of thiopental was 166 ± 56 mg.

Extrapyramidal symptoms were observed in four patients. Although SpO_2 in two patients decreased to 80% just after i.v. flunitrazepam injection, the decrease was transient. Systolic blood pressure in one patient decreased from 129 mmHg to 74 mmHg, 30 min after i.v. flunitrazepam, returning to normal 45 min after drug injection. Thus, no intolerable side-effects appeared in any patients.

DISCUSSION

Because all of the seven hospitals in which the present study was performed, are public psychiatric emergency services, psychiatric emergency patients in the catchment areas were covered. Thus, patients were not selected but were population based, so that the present study has an epidemiological character. Moreover, the total population served by these seven hospitals is 21 420 000, which corresponds to more than one-sixth of the total Japanese population. Thus, the present study is adequate to evaluate the prevalence of use.

The primary outcome of the present study was the prevalence of thiopental use, which was 8.0% in psychiatric emergency patients receiving i.v. medication. Unfortunately, because there has been no previous study on the prevalence or rate of i.v. barbiturate use in a psychiatric emergency situation, it is not possible to say whether the prevalence of thiopental use presented here is a relatively large figure or not. At least, the figure may reflect efforts to reduce thiopental use in Japanese psychiatric emergency situations because i.v. thiopental is not utilized as a first injection and because psychiatrists avoid thiopental use, if possible, even as a second injection.

Remarkably, all of the first injections in patients treated with thiopental were not haloperidol but benzodiazepines, the difference in which was statistically significant. In other words, 12.6% of patients required thiopental following benzodiazepine, whereas no patient required thiopental following haloperidol. Because the present study was naturalistic without randomization, the results may include some bias. The second injection after haloperidol was either benzodiazepine or thiopental, both of which have clinically similar effects. Therefore, the treater may have tended to choose benzodiazepine as a second injection. Meanwhile, the second injection after benzodiazepine was either haloperidol or thiopental, the effects of which are different from each other. Therefore, there may have been greater opportunity to choose thiopental after benzodiazepine injection than after haloperidol injection. The reason for choice of thiopental, however, was that excitement obviously increased following the first injection, which was considered uncontrollable without thiopental according to expert experience. Therefore, the bias mentioned here may have been minimal.

Nevertheless, i.v. thiopental was required only after i.v. benzodiazepine. An explanation is that behavioral disinhibition may have been induced by the initial i.v. benzodiazepine. A previous study also showed that excitement-disinhibition occurred in 5% of i.v. midazolam cases.[13] Furthermore, it has been shown that, to achieve sufficient sedation, a smaller dose of flunitrazepam was required in patients who received haloperidol first followed by flunitrazepam than in patients who received flunitrazepam first followed by haloperidol.[14] The initial haloperidol administration resulted in a small dose of additional benzodiazepine, which may have prevented behavioral disinhibition induced by benzodiazepine. In contrast, the initial injection of i.v. benzodiazepine may have occasionally caused severe behavioral disinhibition that required additional i.v. thiopental.

Thus, in order to reduce the chances of i.v. thiopental in a psychiatric emergency situation, i.v. haloperidol may be superior as an initial injection compared to i.v. benzodiazepine. But benzodiazepine is still the first-line recommendation for i.v. injection as well as haloperidol, because haloperidol cannot be administered to patients with elevation of serum CPK, which is frequently observed in psychiatric emergency patients.[7] In addition, haloperidol has other risks such as laryngeal dystonia and QT prolongation.

A limitation of the present study is that 48% of patients who received i.v. medication were not included due to the difficulty of written informed consent, suggesting a possibility that more severe and complicated cases might not have been included. Therefore, the present findings do not show that i.v. thiopental is not needed for all psychiatric emergency patients. Another limitation is that we could not evaluate behavioral disinhibition itself, because the timing of the second evaluation at 15 min following the first injection appeared to be too late for the evaluation of behavioral disinhibition. An alternative

design targeting behavioral disinhibition induced by i.v. benzodiazepine in a psychiatric emergency situation is needed. Despite methodological limitations, a conservative claim can be made that the choice of i.v. haloperidol as a first injection may reduce the opportunity of i.v. thiopental use in psychiatric emergency situations. Thoughtful treatment decisions on the basis of the present findings may decrease the prevalence of i.v. thiopental use.

ACKNOWLEDGMENTS

The authors wish to thank Dr Michael H. Allen (University of Colorado School of Medicine), Dr Asao Hasegawa (Sato Hospital), Dr Naoya Sugiyama (Yokohama City University), Dr Hiroyuki Nakamura (Department of Environmental and Preventive Medicine, Kanazawa University Graduate School of Medical Science), Dr Kunihiro Isse (Tokyo Metropolitan Toshima General Hospital), Dr Ko Furuta (Tokyo Metropolitan Fuchu General Hospital), Dr Akira Okae (Kyoto Prefecture Rakunan Hospital), Dr Makoto Asano (Chiba Psychiatric Medical Center), and Dr Hisashi Kurosawa (Nippon Medical School), for helpful comments. This work was supported by a grant from the Ministry of Health, Welfare, and Labor of the Japanese Government (Research on Psychiatric and Neurological Diseases and Mental Health, H19-009).

REFERENCES

1 Kälviäinen R, Eriksson K, Parviainen I. Refractory generalised convulsive status epilepticus: A guide to treatment. *CNS Drugs* 2005; 19: 759–768.
2 Minicucci F, Muscas G, Perucca E, Capovilla G, Vigevano F, Tinuper P. Treatment of status epilepticus in adults: Guidelines of the Italian League against Epilepsy. *Epilepsia* 2006; 47 (Suppl. 5): 9–15.
3 Berggren L, Eriksson I. Midazolam for induction of anaesthesia in outpatients: A comparison with thiopentone. *Acta Anaesthesiol. Scand.* 1981; 25: 492–496.
4 Pizov R, Brown RH, Weiss YS *et al.* Wheezing during induction of general anesthesia in patients with and without asthma. A randomized, blinded trial. *Anesthesiology* 1995; 82: 1111–1116.
5 Burburan SM, Xisto DG, Rocco PR. Anaesthetic management in asthma. *Minerva Anestesiol.* 2007; 73: 357–365.
6 Hatta K. Guidelines for tranquilization. In: Japanese Association for Emergency Psychiatry (ed.). *Guidelines for Psychiatric Emergency Treatment, version 2003.* Japanese Association for Emergency Psychiatry, Chiba, 2003; 24–31 (in Japanese).
7 Hatta K, Takahashi T, Nakamura H *et al.* Abnormal physiological conditions in acute schizophrenic patients on emergency admission: Dehydration, hypokalemia, leukocytosis and elevated serum muscle enzymes. *Eur. Arch. Psychiatry Clin. Neurosci.* 1998; 248: 180–188.
8 Key SR, Opler LA, Fiszbein A. *Positive and Negative Syndrome Scale (PANSS) Rating Manual.* Multi-Health System, Toronto, 1991.
9 Breier A, Meehan K, Birkett M *et al.* A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Arch. Gen. Psychiatry* 2002; 59: 441–448.
10 Guy W. *ECDEU Assessment Manual for Psychopharmacology.* US Dept of Health, Education, and Welfare, Bethesda, MD, 1976.
11 Hatta K. Emergency pharmacological management of aggression among agitated psychotic patients in Japan. *Psychiatr. Serv.* 2002; 53: 1077–1078.
12 Inada T. *Evaluation and Diagnosis of Drug-Induced Extrapyramidal Symptoms: Commentary on the DIEPSS and Guide to Its Usage.* Seiwa Shoten Publishers, Tokyo, 1996 (in Japanese).
13 Ibrahim AE, Taraday JK, Kharasch ED. Bispectral index monitoring during sedation with sevoflurane, midazolam, and propofol. *Anesthesiology* 2001; 95: 1151–1159.
14 Hatta K, Nakamura M, Yoshida K *et al.* A prospective naturalistic multicenter study of intravenous medications in behavioral emergencies: Haloperidol versus flunitrazepam. *Psychiatry Res.* 2009. doi:10.1016/j.psychres.2009.03030