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Usefulness of Gabapentin as an Alternative/Adjunct Therapy for Delirium: A Retrospective Observational Study

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Background: Antipsychotics are commonly used to treat delirium but can adversely affect the extrapyramidal and cardiac conduction systems. Antipsychotic use has also been reported to be associated with increased mortality in older adults. Therefore, alternative and adjunct medications for delirium are necessary. We retrospectively assessed the efficacy and safety of gabapentin (GBP) as an alternative and adjunct medication for delirium.

Methods: We retrospectively investigated the records of patients with delirium treated with GBP (71 patients; median age, 81 years; interquartile range, 76-87.5 years; 54.9% males) at a general hospital. We examined duration to delirium improvement, as assessed by the Intensive Care Delirium Screening Checklist (ICDSC) and DSM-5 criteria, as well as adverse events.

Results: The median (interquartile range) GBP dose was 200 mg (150-350 mg)/day. A total of 71.8% and 85.9% of the patients failed to meet the diagnostic criteria for delirium at 2 days and 5 days after initial administration, respectively ($p<0.05$). In subgroup analysis, patients with a history of epilepsy or cerebrovascular disease responded better to GBP than did those without such histories, suggesting that patients with abnormal/borderline neuronal activity respond to GBP even though they do not exhibit seizures. GBP did not induce extrapyramidal symptoms, cardiac conduction disturbances, hyperglycemia, or epilepsy but caused sleepiness and myoclonus.

Conclusions: GBP may improve delirium with fewer adverse effects and may be a safe alternative or adjunct treatment for delirium. Dosage adjustment may be necessary to prevent sleepiness.

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Key words: gabapentin, delirium

Introduction

Delirium is usually treated with antipsychotic drugs. However, balancing the risks and benefits of these drugs is challenging[1–3], as they can cause adverse effects such as extrapyramidal symptoms, especially in patients with Parkinson's disease or related disorders and in older adults[4]. They may also increase the risk of deterioration of cardiac conduction disturbance in patients with heart disease and of hyperglycemia in persons with diabetes.

When these adverse effects are a concern, antidepressants or antiepileptics are used instead of antipsychotics in Japan, as suggested by the Clinical Guideline for the

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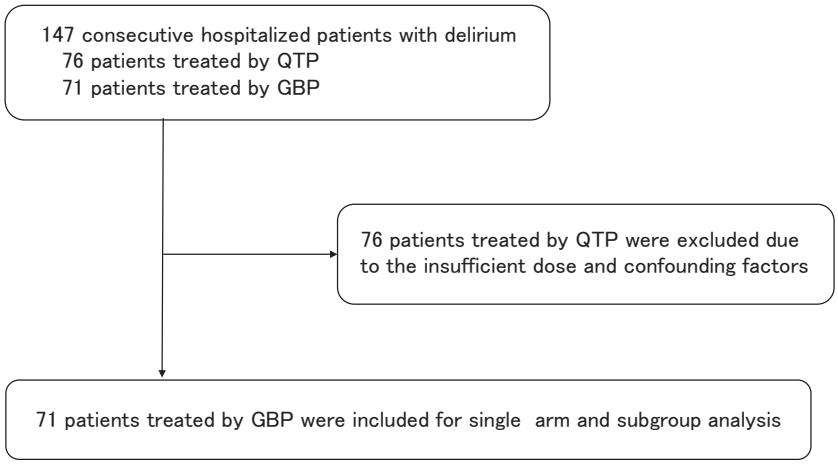

Fig. 1 Flow chart of the retrospective study.
A comparison of gabapentin (GBP) and quetiapine (QTP) was initially attempted, but it was difficult to remove biases and confounding factors. Therefore, single-arm and subgroup analyses of the GBP group were performed.

Treatment of Delirium, published by the Japanese Society of General Hospital Psychiatry[5]. The antiepileptic gabapentin (GBP) is one such drug, although evidence for its efficacy and safety is limited. GBP has been shown to be effective for alcohol withdrawal delirium[6–9], and some reports have shown that GBP prevents perioperative delirium in pediatric patients[10,11]. A prospective study of elderly adults suggested that GBP prevents development of postoperative delirium when administered before surgery[12]. However, there are conflicting reports regarding its efficacy in preventing delirium[13,14]. This discrepancy may be partially attributable to the use of a high-dose GBP regimen that was not adjusted for circadian rhythm. Other possible reasons for this discrepancy may be differences in regular medications, complications, physical condition, age, and biological background. In contrast to conflicting reports from the United States and European countries, a nationwide retrospective cohort study of a Japanese population showed that gabapentinoid use was associated with reduced delirium in older patients undergoing chemotherapy[15]. In addition, a case series of Japanese patients showed that GBP was useful in treating delirium in patients with Parkinson's disease[16]. These reports suggest that interacting factors such as race, comorbidities, and concomitant medications are involved in outcomes.

Moreover, there are few reports on whether GBP improves delirium after its onset[16]. GBP has been reported to be effective against behavioral and psychological symptoms of dementia (BPSD)[17], suggesting that GBP improves psychiatric symptoms of delirium, such as agitation, psychosis, and insomnia, that are similar to BPSD.

Here, we retrospectively investigated data from patients with delirium treated with GBP to examine its efficacy and safety and discuss its potential utility as an alternative to antipsychotics in the treatment of delirium.

Materials and Methods

Using the medical records of Ikeda Municipal Hospital, we retrospectively reviewed data from hospitalized patients with delirium treated with GBP from April 2015 to August 2018. GBP was used for delirium when other anti-delirium drugs were ineffective, or when patients needed to avoid antipsychotics/antidepressants because of their adverse effects. Therefore, treatment with other anti-delirium medicines preceded GBP and was changed to GBP or continued along with GBP in some patients, whereas GBP was used alone in other patients.

We initially reviewed 71 consecutive patients with delirium treated with GBP and 76 patients treated with quetiapine (QTP), excluding those with alcohol withdrawal or hepatic encephalopathy (**Fig. 1**). All patients were of Asian ethnicity. Delirium improvement was greater for the GBP group than for the QTP group (data not shown). However, the daily QTP dose was low (median, 18.75 mg; interquartile range [IQR], 12.5-25 mg), and confounding factors, including indication bias, were difficult to exclude when comparing GBP and QTP. Therefore, only the GBP group was subjected to single-arm and subgroup analyses.

The patients were referred to a liaison consultation team, dementia care team, and palliative care team, and team conferences were held weekly to discuss diagnosis, assessment, and treatment, in addition to daily communi-

Table 1A Background characteristics of patients (N=71)

Male (%)	39 (54.9)
Age (years, median, interquartile range [IQR])	81.0 [76.00-87.50]
Body weight (BW) (kg, median, IQR)	47.7 [40.35-55.35]
Sequential organ failure assessment score (SOFA) (median, IQR)	2.0 [1.0-4.0]
C-reactive protein (CRP) (mg/dL, median, IQR)	3.0 [0.90-7.15]
Cerebrovascular disease (CVD), including head injury (%)	14 (19.7)
Dementia (%)	36 (50.7)
Epilepsy (%)	7 (9.9)
Central nervous diseases other than CVD, dementia, and epilepsy (%)	7 (9.9)
Chronic kidney disease (CKD) (%)	4 (5.6)
Hepatic dysfunction (without hepatic failure) (%)	3 (4.2)
Diabetes mellitus (DM) (%)	19 (26.8)
Pain (%)	24 (33.8)

Table 1B Proportions of patients with precipitating factors that trigger delirium

Electrolyte imbalance (%)	5 (7.0)
Dehydration (%)	8 (11.3)
Renal failure (%)	5 (7.0)
Fracture (%)	7 (9.9)
Heart failure (%)	13 (18.3)
Infection (%)	24 (33.8)
Respiratory failure (%)	37 (52.1)
Operation (%)	13 (18.3)
Anemia (%)	1 (1.4)
Cancer (%)	21 (29.6)
New lesions in central nervous system (%)	2 (2.8)

Table 1C Use of medicines other than gabapentin (GBP)

Anti-delirium drugs (%)	59 (83.1)
Pro-delirium drugs (%)	46 (64.8)
Benzodiazepine receptor agonists (BDZ) (%)	21 (29.6)
Opioids	16 (22.5)

cation. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the Intensive Care Delirium Screening Checklist (ICDSC)[18,19] were used for assessment just before initial administration of the drug (mostly in the evening) and every 24 hours thereafter by team physicians. Delirium was classified as resolved when the ICDSC score reached 3 or lower and symptoms failed to meet DSM-5 criteria. The maximum observation period was 5 days. Missing dropout data were substituted with the last observation carried forward method.

Changes in ICDSC scores in the entire group were analyzed with the Friedman test. A subgroup analysis was performed using the Cox proportional hazards model. EZR Ver.1.53[20] was used for statistical analyses. Adverse events were also examined.

Patients and their guardians were informed of the delirium diagnosis and the possible lack of effectiveness and side effects of antipsychotics and antidepressants. They were also informed of the risks and benefits of off-label GBP use and consented to the therapy. An opt-out approach was used in this study, and participants were included unless they decided to be excluded. Information about the study was provided on our hospital's homepage so that participants could opt out of the project. The patients' names were anonymized, and their privacy was duly protected. This study was approved by the Ethics Committee of the Ikeda Municipal Hospital (approval number: A20009) and conducted in accordance with the principles of the Declaration of Helsinki.

Results

A summary of the patient background and clinical characteristics is shown in **Table 1A**. Age, sex, body weight (BW), general condition, and preexisting conditions, such as cerebrovascular disease (CVD), and including head injury, are presented. The median age was 81 years (IQR, 76.0-87.5 years), 54.9% of patients were male, and median BW was 47.70 kg (IQR, 40.35-55.35 kg). **Table 1B** shows proportions of patients with potential factors that precipitate delirium (i.e., direct triggering factors)[21].

Pro-delirium drugs such as benzodiazepine receptor agonists (BDZ), opioids, steroids, dopamine agonists, and anticholinergic drugs[21] are shown in **Table 1C**. Among them, BDZ and opioids were selected and presented. Anti-delirium drugs such as antipsychotics were used in 83.1% of patients, and GBP was used in most cases when other anti-delirium drugs were ineffective.

As shown in **Table 2A**, the median (IQR) GBP dose was 200 mg (150-350 mg). GBP dose tended to be low owing to the patients' advanced age and low BW; previ-

Table 2A Gabapentin (GBP) dose and interval between onset of delirium and initial administration of GBP

Daily dose (mg, median, IQR) of GBP	200.0 [150.0-350.0]
Time from onset of delirium to initial administration of GBP (days, median, IQR)	3.0 [1.00-7.50]

Table 2B Time course of ICDSC score, dementia improvement, and dropouts (N=71)

	Day 0	Day 2	Day 5
ICDSC score (median, IQR)	7.00 [6.00-8.00]	2.00 [0.00-4.00]	1.00 [0.00-2.00]
	(Friedman chi-square=115.71, df=2, p value=7.49e-26<0.05)		
Number of patients with ICDSC score ≤3 (%)	0 (0)	51 (71.8)	61 (85.9)
Dropouts (%)	0 (0)	3 (4.2)	1 (1.4)

ous US studies of the anti-delirium effect of GBP[12,13] used 900 mg GBP daily for mostly white patients in their 50s through 70s. In Japan, GBP dose ranges from 600-1,800 mg per day for epilepsy and neuropathic pain. The medication was administered mainly at night. The median interval between delirium onset and initial administration of GBP was 3 days, as most patients tried conventional medication before GBP.

We compared ICDSC scores on the initial day (day 0) of administration, after 2 days (day 2), and after 5 days (day 5) (**Table 2B**). The median ICDSC score was 7.00 on day 0, 2.00 on day 2, and 1.00 on day 5 ($P < 0.05$). The ICDSC scores for 71.8% and 85.9% of the patients were equal to or below the cut-off value (ICDSC score=3) for delirium on days 2 and 5, respectively. One and two patients dropped out on day 2 because of treatment ineffectiveness and discharge, respectively. One patient discontinued medication on day 5 because of myoclonus.

In subgroup analyses, improvement was faster for patients with a history of epilepsy and CVD than for other patients (**Table 3A**). Cox proportional hazards analysis of interactions of delirium improvement with each factor revealed that the hazard ratio was relatively high, and the p-value for interaction was lower than 0.2, in patients with a history of epilepsy or CVD (**Table 3B**). Daily dose and the interval between delirium onset and initial administration of GBP also yielded a low p-value for interaction, but the hazard ratio was approximately 1. The initial ICDSC score indicated a low hazard ratio (<1) and a low p-value for interaction.

Adverse events, including extrapyramidal symptoms and related symptoms such as aspiration, falls, and voiding dysfunction, were not observed (**Table 4**). In contrast, GBP caused sleepiness, but no falls were reported. GBP also induces myoclonus in patients undergoing hemodialysis.

Discussion

The present patients were usually treated with anti-delirium agents other than GBP before or in combination with GBP, but their limited effectiveness led to the introduction of GBP. The median duration of delirium before the initial administration of GBP was 3 days (**Table 2A**), suggesting that natural improvement in delirium might have influenced the results. However, GBP may be regarded as efficacious because delirium began to improve immediately after starting GBP, and the reduction in the ICDSC score was statistically significant. Moreover, the interval before starting GBP and using other anti-delirium drugs was not associated with delirium improvement (the hazard ratio was approximately 1 and the p-value was high in subgroup analysis) (**Table 3B**).

Subgroup analysis suggested an interaction of delirium improvement (efficacy of GBP) with a history of epilepsy or CVD (**Table 3B**). Namely, delirium was more likely to improve in patients with a history of epilepsy or CVD than in those without such a history, even though seizures were not observed during the observational period. This suggests that GBP may work differently from antipsychotics and that it acts on abnormal/excessive neuronal activity or irritability in delirium, regardless of the presence of active seizures. GBP may also be useful for non-convulsive seizures that resemble delirium because GBP, unlike antipsychotics, does not lower seizure thresholds in patients with epilepsy.

Daily dose and the interval from delirium onset to initial administration of GBP had a low p-value for interaction. However, the hazard ratio was approximately 1, suggesting these variables were not associated with clinical improvement in delirium. The initial ICDSC score in-

Table 3A Number and characteristics of patients with an ICDSC score ≤3 (%)

		Day 0	Day 2	Day 5
Backgrounds	Sex (Male) (N=39)	0	28 (71.8)	33 (84.6)
	CVD (N=14)	0	12 (85.7)	14 (100.0)
	Dementia (N=36)	0	24 (66.7)	31 (86.1)
	Epilepsy (N=7)	0	7 (100.0)	7 (100.0)
	Central nervous diseases other than CVD, dementia, and epilepsy (N=7)	0	4 (57.1)	5 (71.4)
	CKD (N=4)	0	3 (75.0)	3 (75.0)
	Hepatic dysfunction (N=3)	0	1 (33.3)	3 (100.0)
	DM (N=19)	0	14 (73.7)	17 (89.5)
	Pain (N=24)	0	17 (70.8)	19 (79.2)
Precipitating factors	Electrolyte imbalance (N=5)	0	3 (60.0)	4 (80.0)
	Dehydration (N=8)	0	6 (75.0)	8 (100.0)
	Renal Failure (N=5)	0	3 (60.0)	3 (60.0)
	Fracture (N=7)	0	4 (57.1)	5 (71.4)
	Heart Failure (N=13)	0	12 (92.3)	13 (100.0)
	Infection (N=24)	0	16 (66.7)	22 (91.7)
	Respiratory failure (N=37)	0	28 (75.7)	32 (86.5)
	Operation (N=13)	0	9 (69.2)	11 (84.6)
	Anemia (N=1)	0	1 (100.0)	1 (100.0)
	Cancer (N=21)	0	17 (81.0)	17 (81.0)
	New lesions in the central nervous system (N=2)	0	1 (50.0)	2 (100.0)
Drugs other than GBP	Anti-delirium drugs (N=59)	0	42 (71.2)	50 (84.7)
	Pro-delirium drugs (N=46)	0	33 (71.7)	37 (80.4)
	BDZ (N=21)	0	15 (71.4)	16 (76.2)
	Opioids (N=16)	0	11 (68.8)	12 (75.0)

dicated a low hazard ratio and p-value for the interaction, indicating that the effectiveness of GBP was lower in those with severe delirium.

The mechanism of delirium is unclear. Excessive dopaminergic neuron activity is hypothesized and is the rationale for using antipsychotics[22]. Notably, GBP works differently from antipsychotics[23–25]. Therefore, it is still unknown how GBP functions in abating delirium. GBP does not affect dopamine receptors and acts on gamma-aminobutyric acid (GABA) and glutamate systems and may increase GABA levels in the ventrolateral preoptic nucleus (VLPO), the center of sleep, thereby improving sleep[26,27]. Furthermore, GBP may potentiate GABAergic interneurons by increasing GABA and might control excitatory neurons such as dopaminergic or glutaminergic neurons, which are thought to be excessively activated in delirium[22]. GBP also suppresses the activity of glutaminergic neurons via presynaptic inhibition of calcium ion channel α2δ subunits. Unlike BDZ, GBP does not bind to or modulate gamma-aminobutyric acid type A (GABAA) receptors and does not directly block dopamine D2 or *N*-methyl-D-aspartate (NMDA) receptors. Therefore, GBP may act naturally without artificial modulation or blocking of neurotransmitter receptors.

It is unclear whether GBP causes dependence and whether it is beneficial for treating substance dependence[28–31] but it is rarely addictive in the general population. Addiction has been reported in patients with a history of substance use disorder and when GBP is used in combination with preexisting addictive substances[29,30]. GBP can be considered beneficial when administered at a duly prescribed and monitored dosage. In any event, these concerns should not hinder use of GBP for delirium, because delirium treatment is typically short.

GBP did not cause extrapyramidal or related symptoms such as aspiration, falls, and voiding dysfunction (**Table 4**), which is consistent with the fact that GBP does not affect dopamine receptors. No exacerbation or induction of cardiac conduction disorders or hyperglycemia was observed. Therefore, GBP can be safely used in patients with Parkinson's disease, heart disease, and diabetes mellitus.

Regarding its adverse effects, GBP causes somnolence and is believed to increase GABA in the VLPO, as mentioned, which suggests that it can improve sleep. However, GBP could induce a daytime hangover, necessitat-

Table 3B Results of subgroup analysis

	Hazard ratio	95%CI	P for Interaction
Sex	1.047	0.6323 - 1.734	0.8584
Age	0.9960	0.9689 - 1.024	0.7782
BW	1.001	0.9774 - 1.024	0.9643
SOFA	1.008	0.8539 - 1.191	0.9212
CRP	0.9848	0.9357 - 1.037	0.5586
CVD	1.584	0.8667 - 2.893	0.1350
Dementia	0.8015	0.4801 - 1.338	0.3974
Epilepsy	1.717	0.7707 - 3.823	0.1860
Central nervous diseases other than CVD, dementia, and epilepsy	0.6847	0.2735 - 1.714	0.4185
CKD	1.113	0.3471 - 3.571	0.8567
Hepatic dysfunction	0.8723	0.2719 - 2.798	0.8183
DM	1.017	0.5807 - 1.781	0.9531
Pain	0.9357	0.5422 - 1.615	0.8112
Electrolyte imbalance	0.9031	0.3271 - 2.494	0.8441
Dehydration	1.307	0.6208 - 2.751	0.4811
Renal failure	0.6650	0.2080 - 2.126	0.4914
Fracture	0.7194	0.2877 - 1.799	0.4813
Heart failure	1.428	0.7651 - 2.667	0.2630
Infection	0.9427	0.5579 - 1.593	0.8257
Respiratory failure	1.006	0.6074 - 1.667	0.9803
Operation	0.9652	0.5017 - 1.857	0.9156
Anemia	2.059	0.2818 - 15.04	0.4766
Cancer	1.132	0.6408 - 1.998	0.6700
New lesions in the central nervous system	1.166	0.2837 - 4.793	0.8312
Anti-delirium drugs	0.9786	0.5081 - 1.885	0.9484
Pro-delirium drugs	0.9231	0.5507 - 1.547	0.7613
BDZ	0.8942	0.5047 - 1.584	0.7017
Opioids	0.8319	0.4404 - 1.571	0.5706
Dosage per day	0.9987	0.9968 - 1.001	0.1823
Time between the onset of delirium and the initial administration of GBP	1.027	0.9919 - 1.063	0.1348
Initial ICDSC score	0.8070	0.6488 - 1.004	0.05401

Table 4 Adverse events

Aspiration (%)	0 (0)
Extrapyramidal symptoms (%)	0 (0)
Fall (%)	0 (0)
Myoclonus (%)	1 (1.4)
Somnolence (%)	11 (15.5)
Voiding dysfunction (%)	0 (0)
Exacerbation or induction of hyperglycemia (%)	0 (0)
Exacerbation or induction of cardiac conduction disorders (%)	0 (0)
Hyperglycemia (%)	0 (0)

ing dose adjustment.

One patient with chronic kidney disease presented with myoclonus. GBP was reported to cause or exacerbate myoclonus[32]. The dose should be reduced in patients with severe kidney dysfunction, because the area under the blood concentration curve tends to increase. Unfortunately, regardless of GBP use, patients with severe kidney disease are prone to developing myoclonus. Therefore, GBP should be used carefully in patients with severe kidney disease, because it can cause myoclonus, somnolence, and other adverse effects.

Another benefit of GBP is that it does not undergo he-

patic metabolism and thus does not burden the liver or interfere with the metabolism of other drugs (e.g., cytochrome P450 metabolism).

This study has several limitations. First, it was a single-arm, uncontrolled, and nonrandomized study and therefore cannot exclude the effects of confounding factors. A prospective randomized controlled trial is necessary to avoid the effects of confounding factors, including confounding by indication. Second, the sample was small and not sufficient for robust subgroup analyses.

In conclusion, the present findings suggest that GBP is likely to be an effective and safe alternative or adjunct therapy to antipsychotics for the treatment of delirium. However, the dose should be adjusted to reduce somnolence, and GBP should be used carefully in patients with severe kidney disease or myoclonus.

Conflict of Interest: One author (HT) received a research grant from Pfizer. The other authors declare no conflict of interest concerning this study.

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