Original Article

Rapid Relief of Catatonia in Mood Disorder by Lorazepam and Diazepam

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Background: Catatonia has risks of severe morbidity and mortality and needs early treatment. In this study, we investigated more patients to discuss the efficacy of this treatment in patients with major depressive disorder (MDD) or bipolar I disorder (BPI).

Methods: During a period of 9 years, we identified 12 catatonic patients with mood disorder, with MDD (n = 10) and BPI (n = 2) in the emergency department, inpatient and outpatient units of a general hospital. The patients received intramuscular injection (IMI) of 2 mg lorazepam once or twice during the first 2 h. If intramuscular lorazepam failed, intravenous dripping (IVD) of 10 mg diazepam in 500 mL normal saline every 8 h for 1 day was prescribed.

Results: Eight patients had full remission of catatonia after receiving one dose of 2 mg lorazepam IMI. Two patients needed two doses of 2 mg lorazepam IMI. Two patients with BPI recovered from catatonia using one dose of 10 mg diazepam IVD over 8 h after they failed to respond to two doses of 2 mg lorazepam IMI. The response rate to lorazepam IMI was 83.3%. All catatonic features remitted in 24 h with 100% response rate.

Conclusions: The lorazepam–diazepam treatment strategy is a safe and effective method to relieve catatonia in mood disorder within 1 day. Psychiatrist consultation is helpful for final diagnosis and rapid treatment of catatonia.

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Key words: bipolar I disorder, catatonia, lorazepam, major depressive disorder

At a Glance Commentary

Scientific background of the subject

Electroconvulsive therapy (ECT) is effective to treat catatonia. Benzodiazepine also has effect to relieve catatonia with less serious complications.

What this study adds to the field

The lorazepam–diazepam treatment strategy is a safe and effective method to rapidly relieve catatonia in mood disorder.

Kahlbaum described catatonia as a syndrome of motor dysfunction including mutism, immobility, staring gaze, negativism, stereotyped behavior, waxy flexibility, and verbigeration in 1874.[1] Catatonia is expressed in 10% of psychiatric inpatients and is more common in patients with mood disorder than those with schizophrenia.[2] Abrams and Taylor studied 55 psychiatric inpatients with catatonic features and reported 25% patients had schizophrenia and more than 66% had mood disorder, especially mania.[3] Catatonia also can occur in a wide range of illnesses, including drug intoxications,[4,5] drug withdrawals,[6] neurological disorders, and other general medical conditions,[7,8] including renal or hepatic dysfunction,[9,10] autoimmune disease, and infection.[11,12] Persistent catatonic symptoms have risks of pulmonary embolism and related severe morbidity and mortality.[13,14] Therefore, early recognition and rapid treatment of catatonia to prevent the complications are clinically important.

Studies in the past have used benzodiazepines (BZDs) which included lorazepam, diazepam, and midazolam to resolve catatonia.[15-17] Rosebush *et al*., revealed that 12 out of 15 catatonic patients have full remission to oral 1-2 mg lorazepam in 2 h.[18] In a prospective and open study, Ungvari et al, revealed that low dose of oral lorazepam or intramuscular diazepam is significantly effective in treating 16 out of

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18 catatonic patients in 48 h.[19] Electroconvulsive therapy (ECT) is also effective as the first-line treatment strategy to relieve catatonia or as the second-line treatment if a BZD fails.[20] Bush *et al.* and Fink showed that ECT is effective in relieving catatonia after failure of using 6-16 mg/day lorazepam for up to 5 days.[21] ECT is a safe treatment, although serious complications including status epilepticus, prolonged seizure, postictal agitation, cardiovascular compromise, and pulmonary embolism are reported infrequently.[22,23]

In Chang Gung Memorial Hospital, lorazepam intramuscular injection (IMI) has been used to treat catatonia in Chinese ethic Taiwanese patients since 1999.[24] In addition to the impressive remission from catatonic status while using lorazepam IMI, we also found that diazepam intravenous dripping (IVD) had treatment efficacy in some catatonic patients while lorazepam IMI failed.[24] Lorazepam IMI or diazepam IVD could be used, rather than ECT, to treat catatonia. Huang used a lorazepam–diazepam treatment strategy to relieve catatonia rapidly in patients with schizophrenia and major depressive disorder (MDD).[24,25] In this study, we collected more patient data since our last report to investigate the efficacy of this treatment strategy in catatonic patients with MDD and bipolar I disorder (BPI).

METHODS

We collected and analyzed data retrospectively from the medical charts of catatonic patients with mood disorder (MDD and Bipolar), who received psychiatric intervention in the emergency department, or consultation services, and in both inpatient and outpatient units of one medical center in Southern Taiwan between 2002 and 2011. The institutional review board of Chang Gung Memorial Hospital approved the study. Two psychiatrists (one resident and one experienced psychiatrist) interviewed the patients and made the definite diagnosis. The psychiatrists used Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as the basis for the diagnosis of catatonia. Patients who showed at least two of the following five criteria were included: Motor immobility (including waxy flexibility) or stupor, excessive motor activity, extreme negativism or mutism, peculiarities in voluntary movement, and echolalia or echopraxia. In this study, we excluded patients who were reported previously.[25]

After making the diagnosis of catatonia, the following lorazepam–diazepam treatment strategy was performed to treat catatonia: (A) IMI, 1 ampule (2 mg/mL per ampule); (B) if the patient failed to respond to the first dose of lorazepam IMI, repeat one dose of lorazepam IMI, 1 ampule, within 2 h; (C) if the above two doses of lorazepam IMI were ineffective, diazepam IVD every 8 h was prescribed (10 mg/2 mL per ampule, infused in 500 mL per bottle concentration of normal saline); (D) until the remission of catatonia, all patients were drug-free except the above lorazepam or diazepam use. The epidemiologic data and the treatment response toward lorazepam–diazepam treatment strategy of the patients were analyzed and discussed.

The definition of treatment response was that the patients had no further catatonic features as DSM-IV criteria and they could move and communicate with the psychiatrists.

RESULTS

Over a period of 9 years, we identified 12 patients in mood disorder with catatonic features, including 10 patients having MDD (2 men, 8 women) and two patients having BPI (1 man, 1 woman). Table 1 shows the demographic data and treatment responses to lorazepam–diazepam treatment strategy for MDD and BPI. The age of the patients ranged from 21 to 66 (42.83 ± 13.96) years. Eight patients had full remission of catatonia after receiving one dose of 2 mg lorazepam IMI (Median ± SD, 43.12 ± 16.14 years). Two patients needed two doses of 2 mg lorazepam IMI (Median ± SD, 46.50 ± 9.19 years). Two patients with BPI recovered from catatonia by using one dose of continuous IVD of 10 mg diazepam over 8 h after they failed to respond to two doses of 2 mg lorazepam IMI (Median ± SD, 38.00 ± 12.73 years). The response rate to lorazepam IMI in a dose of 2–4 mg was 10 (83.3%) per 12 patients. All catatonic features remitted in 24 h with 100% response rate by this lorazepam–diazepam treatment strategy.

The catatonic features in these patients included stupor consciousness (n = 12, 100%), mutism (n = 12, 100%), negativism (n = 4, 33%), purposeless excitement (n = 3, 25%), waxy flexibility (n = 1, 8%), posturing (n = 1, 8%), stereotyped behavior (n = 1, 8%), echopraxia (n = 1, 8%), and immobility (n = 1, 8%) [Table 1].

The facilities that catatonic patients received as the psychiatrist intervention included emergent room for seven patients (58%), neurology unit for one patient, plastic surgery unit for one patient, psychiatric clinic for two patients, and psychiatric unit for one patient [Table 1].

DISCUSSION

In this study, the response rate of treating catatonia by using IMI of 2-4 mg lorazepam was 10 (83.3%) per 12 patients [Table 1]. All catatonic features of the patients remitted within 24 h with this lorazepam–diazepam treatment strategy. The response rate within 1 day was 100%. The response rate with lorazepam was slightly lower than that in our previous research on MDD (lorazepam response rate 85.7% and 1-day response rate 100%).[25]

The risk factors for catatonia in depression are increasing age, higher frequency of major depressive episodes,

Table 1: Demographic data and treatment response to lorazepam-diazepam treatment strategy in mood disorder with catatonia

Patient	Age (years)	Sex	Previous psychiatric diagnosis	Duration	Final psychiatric diagnosis		Facility	Catatonic symptoms and signs besides stupor and mutism	Number of receiving lorazepam IMI	Number of receiving diazepam IVD
					MDD	BPI				
1	21	M	AD	1 month	+	-	Neurology ward	Nil	1	Not used
2	28	F	MDD	1 year	+	-	ER	Nil	1	Not used
3	55	F	None		+	-	ER	Negativism, purposeless excitement	1	Not used
4	66	F	None		+	-	ER	Negativism, posturing	1	Not used
5	57	F	None		+	-	ER	Nil	1	Not used
6	33	M	MDD	15 years	+	-	Plastic surgery ward	Echopraxia, purposelessness excitement	1	Not used
7	51	F	MDD	3 years	+	-	Psychiatry OPD	Nil	1	Not used
8	34	F	MDD	1 year	+	-	ER	Nil	1	Not used
9	53	F	MDD	6 years	+	-	ER	Waxy flexibility, stereotyped behavior	2	Not used
10	40	F	None		+	-	ER	Negativism	2	Not used
11	29	F	None		-	+	Psychiatry OPD	Purposelessness excitement	2	1
12	47	M	BPI	22 years	-	+	Psychiatry ward	Negativism, immobility	2	1

Abbreviations: AD: Adjustment disorder; MDD: Major depressive disorder; BPI: Bipolar I disorder; IMI: Intramuscular injection; IVD: Intravenous dripping; OPD: Out-patient department

more severe impairment in cognitive function and daily activity.[26] In this study, we had no data of non-catatonia patients in MDD to investigate the age distribution between catatonia and non-catatonia groups. But while comparing the differences in response rate to lorazepam IMI in catatonic patients with MDD, the median age of patients who responded to two doses of 2 mg lorazepam IMI was older than those who responded to one dose. In catatonic patients with MDD, 80% responded to one dose of 2 mg lorazepam IMI and 20% responded to two doses of 2 mg lorazepam IMI. However, other catatonia rating scales are needed to further assess the severity of catatonic features more thoroughly and investigate the relationship between the catatonia features and the response rate to lorazepam IMI. Besides, 60% of MDD patients with catatonic features had previous psychiatric diagnoses (one patient with adjustment disorder, five patients with MDD).

We found that all MDD patients in this study had 100% response rate to lorazepam IMI, although two patients with BPI (Case No. 11 and 12 in Table 1) failed. One female catatonic patient with BPI (Case No. 11) had episodes of recurrent catatonia. She had initial response to two doses of 2 mg lorazepam IMI during the first catatonic episode. While recurrent catatonia occurred, we used one dose of 10 mg diazepam IVD directly rather than lorazepam IMI to resolve episodes of recurrent catatonia completely according to the treatment strategy. One male bipolar patient (Case No. 12) had poor response to lorazepam IMI and also needed one dose of diazepam IVD to alleviate catatonia. The results of this study may indicate that the catatonic features in MDD showed better response to lorazepam IMI than those in BPI. However, the mechanism is still unknown.

More than 25% of mania patients had catatonic features and more than 20% of catatonic patients were associated with mania.[2] In this study, the prevalence of BPI was 17%, which is smaller than that in the previous reports. Catatonic features in BPI may be underestimated or misdiagnosed.[27] Long-term follow-up is needed to observe the patient's clinical course of mood disorder.

Neurotransmitter disturbance has been hypothesized to explain the mechanism of catatonia, although the definite cause has not been clarified. Northoff *et al.*, illustrated a top-down modulation of basal ganglion with brain image evidence of decreased receptors of inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the left sensorimotor cortex in catatonic patients.[28-30] On the other hand, the dysfunction of primary excitatory neurotransmitter, glutamate, has been suggested in catatonia,[31,32] and glutamate antagonist, amantadine, may have adjunctive effect in treating catatonia.[33] Massive dopamine blockage suddenly may cause catatonia, neuroleptic malignant syndrome-like, and may explain the dopamine receptor antagonists have no general efficacy to treatment catatonia.[34] BZD, through the mechanism of GABA agonist, showed reliable treatment efficacy to catatonic patients in mood disorder, and it may also indicate the association of

GABA and catatonic features in mood disorder. Among the different BZDs, lorazepam has a role as the first-line treatment to acute catatonia and in maintenance treatment to prevent relapse.[35-37] Diazepam was also reported to have efficacy in treating catatonia.[16,38] In this study, two patients responded to 10 mg diazepam IVD after two doses of 2 mg lorazepam IMI failed to relieve their catatonia. It needs further study to investigate the different mechanisms operating between lorazepam and diazepam in treating catatonia, even though both of them have similar effect to modulate GABA via BZD receptors.

The distribution percentage of catatonic signs in mood disorder in this study was similar to the report of Rosebush *et al.*, which demonstrated that 46% catatonic patients have comorbid mood disorder with 55–65% symptoms of mutism and withdrawal and unusual features of waxy flexibility, stereotyped behavior, and echopraxia.[39] In schizophrenic patients, higher prevalence of posturing and stereotyped behavior is reported.[40]

There are limitations of this study. A major limitation is the design of retrospective chart review. There was no control group to compare to the treatment group. The results cannot conclude that this lorazepam–diazepam treatment strategy is the most effective treatment for catatonic patients in mood disorder. Double-blind, controlled prospective study is needed to investigate the reliability in the future. Secondly, the sample size was small. The study comprised catatonic patients in one medical center, and the results cannot be generalized to all catatonic patients in mood disorder.

In conclusion, we found that lorazepam–diazepam treatment strategy is a safe and effective method to relieve catatonic patients in mood disorder within 1 day. Psychiatrist consultation is helpful for final diagnosis and rapid treatment of catatonia.

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