Immediate Effect of Intravenous Diazepam in Neuroleptic-Induced Acute Akathisia: An Open-Label Study

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Background: Neuroleptic-induced akathisia can be severely distressing to some patients, and rapid treatment would be preferable. However, there have been relatively few studies conducted regarding the rapid treatment of akathisia. The effect of intravenous diazepam at the beginning of treatment for akathisia was studied in an open clinical trial.

Method: The subjects were 18 patients with schizophrenia or bipolar I disorder (DSM-IV criteria) who developed neuroleptic-induced acute akathisia during antipsychotic medication and who required immediate relief from the distress of akathisia. Diazepam was given intravenously to the patients at a rate of 5 mg per 30 seconds.

Results: All 18 subjects experienced immediate relief from akathisia after the injection of diazepam (mean ± SD dose = 12.6 ± 2.6 mg; range, 10–17 mg). They reported no serious adverse effects.

Conclusion: The results suggest that intravenous diazepam could be used in the treatment of patients with severely distressing akathisia who require immediate relief.

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Akathisia is a common neurologic side effect produced by antipsychotic therapy,[1–3] although the more prevalent use of atypical antipsychotic drugs has led to a decrease in the reported incidence of akathisia.[4–6] However, conventional or typical antipsychotic drugs are still used by many clinicians. In addition, risperidone, a commonly prescribed agent originally classified as an atypical antipsychotic, produces akathisia at a frequency similar to that reported for typical antipsychotic drugs.[7–9]

Akathisia generally consists of a subjective feeling of inner restlessness and objective restless movements. The feeling of inner restlessness can be severely distressing to the patient.[10,11] Therefore, once akathisia is diagnosed, rapid relief would be of benefit to the patient. However, there have been relatively few studies published that focus on a rapid treatment for the amelioration of distressing akathisia. This study reports the effect of intravenous (IV) diazepam on neuroleptic-induced acute akathisia when rapid relief was required.

METHOD

The studies were carried out in an open clinical trial at Fukui Prefectural Hospital between January 1997 and July 1998. The study subjects were inpatients or outpatients receiving antipsychotic treatment who met the diagnostic criteria of the DSM-IV[12] for schizophrenia or bipolar I disorder by clinical interview and were under the care of one of the authors (S.H.) during the aforementioned period.

The neuroleptic-induced acute akathisia was clinically diagnosed by one of the authors (S.H.) on the basis of the research criteria in Appendix B of the DSM-IV.[12] Subjective inner restlessness was identified by carefully interviewing the patients. Objective restless movements were observed in the consulting room or identified from the information provided by the patients and their family members. After akathisia was diagnosed, the patients were asked whether they required immediate relief of the distress or were able to wait a few hours or more to obtain relief. In the subjects who required immediate amelioration of the distress, the severity of subjective distress was rated using the subjective items of the Barnes Akathisia Scale[13]: awareness of restlessness and distress related to restlessness. In addition, the objective item and global clinical assessment (GCA) item were rated for reference.

The subjects who required immediate amelioration of the distress and had a subjective item of awareness score ≥ 2 and a distress score ≥ 2 were enrolled in the study. The subjects who did not require immediate relief or consent to IV injection, as well as the patients who did not clearly communicate their subjective inner feelings to one of the authors (S.H.), were excluded from the study. Subjects

were also excluded if they had a history of or a current contraindication to IV diazepam such as obstructive pulmonary diseases that may induce apnea.

Consequently, eighteen patients (11 inpatients and 7 outpatients), 10 men and 8 women, mean ± SD age = 31.3 ± 8.0 years (range, 20–50 years) were included in this study. The mean ± SD scores of the subjective awareness and distress items, the objective item, and the GCA item before injection were 2.7 ± 0.42, 2.7 ± 0.42, 2.7 ± 0.42, and 4.7 ± 0.42, respectively. All subjects received IV diazepam within 24 hours of the appearance of akathisia.

After informed consent was obtained from the patients for the administration of IV diazepam, diazepam was injected into the median cubital vein at a rate of about 5 mg per 30 seconds. The patients were continuously asked about their subjective restlessness and distress during the injection. The injection of diazepam was to be terminated when the patients acknowledged the disappearance of their subjective distress related to restlessness or the appearance of severe side effects (e.g., apnea) or when the IV dose of diazepam reached 20 mg.

The patients were lying on a bed during the injection and were instructed not to move until the injection was finished. Subjective restlessness alone was rated during injection as motor restlessness cannot be accurately rated in that situation. After the injection was finished and the patients were allowed to move freely, motor restlessness was observed for about half an hour and the objective item and GCA item were rated. Subsequently, the course of the symptoms in inpatients continued to be observed by the staff in the wards. The course of the symptoms in outpatients following their return home was reported by the patients and family members.

Subjects were asked during and after the injection if they experienced the following side effects known to occur after diazepam administration: drowsiness, fatigue, ataxia, and dizziness, as well as other undefined side effects. Blood pressure and pulse rate were measured before and after the injection. Artificial ventilation and IV flumazenil were to be provided if apnea appeared.

Following the injection of diazepam, usual antiakathisia measures were implemented in all subjects, including a reduction in the dose of the prescribed antipsychotic or switching to a lower-potency antipsychotic, if possible, and the addition of oral anticholinergics, benzodiazepines, or β-blockers to their daily medication regimen.

RESULTS

The IV injection of diazepam completely ameliorated the subjective restlessness and distress of antipsychotic-induced akathisia in all 18 patients. Although the injection of diazepam was stopped when the patients' subjective restlessness disappeared, the objective restless movements were also absent after the termination of the injection in all subjects. Thus, the subjective restlessness and distress scores and objective score were reduced from 2 or 3 to 0 and the GCA score was reduced from 4 or 5 to 0 in all 18 subjects after the injection. The mean ± SD dose of diazepam that was needed to completely ameliorate akathisia was 12.6 ± 2.3 mg (range, 10–17 mg). Twelve subjects reported side effects after the injection, which included slight or mild drowsiness, dizziness, ataxia, and malaise. These side effects were transient, disappearing within 30 minutes to 2 hours after the injection, and had no serious clinical effects. Apnea did not occur in any of the subjects and thus artificial ventilation and flumazenil were not required. The IV injection of diazepam did not produce any significant alteration in blood pressure or pulse rate. Akathisia was completely ameliorated for at least 3 hours in all subjects. Akathisia reappeared in 8 subjects 3 to 24 hours after the first injection of diazepam, and 6 of the 8 subjects received further increase of the dose of antiakathisia agents, further reduction of the dose of antipsychotic, or switch to a lower-potency antipsychotic following reappearance of akathisia. Five of the 8 in whom akathisia reappeared required 1 to 3 additional injections of diazepam to treat the relapse of akathisia; additional IV diazepam was not given to the 3 subjects for whom the intensity of akathisia was milder than before diazepam treatment, and akathisia disappeared in these subjects without further addition of IV diazepam. The remaining 10 subjects continued to experience complete relief with the first injection of diazepam and the subsequent usual antiakathisia measures. A summary of patient demographics, medication regimens, subjective and objective ratings, and medication side effects is listed in Table 1.

DISCUSSION

A number of pharmacologic and nonpharmacologic approaches have been utilized for the treatment of neuroleptic-induced acute akathisia.[11,14] Effective interventions include reducing the dosage of neuroleptic if possible or switching to a lower-potency neuroleptic.[15] However, a period of several days to a week may be required for the complete cessation of akathisia with the above interventions.[15,16] The administration of oral anticholinergics, benzodiazepines, or β-blockers is considered to be effective for akathisia, but there is a delay in onset in their therapeutic effect.[17–19] For example, it may take several to 48 hours for the onset of the beneficial effects of β-blockers, which have been reported to produce the most rapid effect among the orally administered agents.[11,19,20] Thus, intervention via the oral route requires several hours or more to be effective. This time lag may be intolerable to some patients who want immediate relief of distress. Desire for relief is immediate because akathisia is subjectively severely distressing. The severity can

Table 1. Patient Demographics, Medication Regimens, and Medication Side Effects After Injection in Patients With Neuroleptic-Induced Acute Akathisia[a]

No.	Age	Sex	Illness	Medication Before Injection (mg)	Medication Duration (days)[b]	Subjective Score	Distress Score	GCA Score	Diazepam IV Dosage (mg)	Side Effects After Injection	Total No. of Times of Injection	Final Medication (mg)[c]
1	35	M	S	Ris (12), Bip (3), Flu (2)	8	3	3	5	11	…	2	Ris (9), Bip (9), Bro (15), Flu (2)
2	20	F	S	Hal (4.5), Bip (2), Flu (2)	1	3	3	5	10	Drowsiness	1	Hal (4.5), Bip (6), Bro (6), Flu (2)
3	26	M	S	Hal (12), Bip (3)	21	3	3	5	10	…	1	Hal (12), Bip (9), Bro (15)
4	32	M	S	Hal (14), Bip (3)	18	3	3	5	13	Dizziness	1	Hal (9), Bip (9), Bro (6)
5	39	M	BP	Hal (6), Bip (3), Lit (1200), Flu (4)	10	2	2	4	12	Drowsiness	1	Zot (50), Bip (6), Bro (15) Lit (1200), Flu (4)
6	26	M	S	Ris (12), Bip (3)	7	3	3	5	15	Drowsiness	2	Ris (12), Bip (9), Bro (15)
7	33	M	S	Ris (6), Bip (2)	7	3	3	5	12	Ataxia	4	Zot (75), Bip (9), Bro (15), Pro (60)
8	21	F	S	Hal (3), Bip (2)	12	3	3	5	10	Ataxia	1	Hal (3), Bip (6), Bro (6)
9	50	M	S	Ris (9)	3	3	3	5	12	Drowsiness	1	Ris (9), Bip (9), Bro (6)
10	41	F	S	Hal (4.5)	14	3	3	5	10	…	1	Hal (4.5), Bip (9)
11	26	F	S	Ris (6), Bip (3)	6	2	2	4	15	Dizziness	1	Ris (5), Bip (6), Bro (6)
12	42	F	S	Ris (9), Flu (2)	10	3	3	5	10	…	1	Ris(6), Flu (2), Bip (9), Bro (6)
13	33	F	S	Hal (18), Bip (6), Flu (2)	13	3	3	5	11	…	3	Hal (9), Bip (9), Pro (40), Bro (15), Eth (4), Flu (2)
14	25	M	S	Hal (18), Bip (3)	11	3	3	5	17	Drowsiness	1	Hal (12), Bip (9), Bro (6)
15	29	F	S	Hal (12), Flu (4)	8	3	3	5	13	…	1	Hal (12), Flu (4), Bip (9), Bro (15)
16	36	M	S	Ris (9)	6	2	2	4	11	Drowsiness	2	Ris (6), Bip (9), Bro (15)
17	27	F	BP	Hal (6), Lit (1200)	7	2	2	4	16	Ataxia, malaise	1	Hal (6), Lit (1200), Bip (9), Bro (6)
18	24	M	S	Ris (3)	3	3	3	5	15	Ataxia	1	Ris (3), Bip (6), Bro (6)

[a]Abbreviations: Bip = biperiden, BP = bipolar disorder, Bro = bromazepam, Eth = ethyl loflazepate, Flu = flunitrazepam, GCA = global clinical assessment item of Barnes Akathisia Scale, Hal = haloperidol, Lit = lithium, Pro = propranolol, Ris = risperidone, S = schizophrenia, Zot = zotepine.
[b]Medication duration = the number of consecutive days during which the patients were taking the listed medications prior to diazepam injection.
[c]Final medication = oral medication regimen that eventually controlled akathisia completely without further addition of IV diazepam.

occur to the extent that the patient wants to die to escape the distress of akathisia.[21–24]

One potential strategy would be to administer antiakathisia agents via the IV route, which should theoretically produce a more rapid response compared with the oral route. Previously, it has been reported that the IV administration of diazepam did not completely ameliorate akathisia until 1 hour after administration.[25] The delayed onset reported by the aforementioned study may be related to the usage of a lower dose of diazepam (5 mg) compared with the present study. In our study, akathisia was immediately ameliorated in all 18 patients following the IV injection of 10 to 17 mg of diazepam. To our knowledge, no previous study has reported such a rapid response. However, two thirds of the patients developed signs of benzodiazepine intoxication (i.e., sedation, drowsiness, and ataxia). Thus, it is possible that the antiakathisia effects of IV diazepam were related to its nonspecific sedation.

It was reported that the intensity of akathisia decreases when the patient performs a task that requires concentration.[21] Therefore, the immediate improvement during IV injection of diazepam may have been related to the patients' concentrating on the task. However, the amelioration continued for at least 3 hours in all subjects. This finding suggests that the amelioration is due to the effect of diazepam rather than the effect of the patients' concentrating during the injection. However, the intensity of akathisia fluctuates during the course.[12,21] Thus, it cannot be ruled out that the natural fluctuation of intensity of akathisia during the course contributed, to a certain extent, to the abatement of distress following the injection.

Although the side effects elicited by IV diazepam are not insignificant, the benefits of the rapid and effective amelioration of akathisia were considered to outweigh the side effects reported. In fact, all of the patients welcomed the rapid effect produced by the IV administration of diazepam. Five patients required an additional injection of diazepam following the reappearance of akathisia. However, after the complete cessation of akathisia, none of the patients required an additional injection of diazepam. Given that benzodiazepines have some potential for addiction, one might argue that patients might request an additional injection as they experienced euphoria or hedonia after the first injection. However, this is unlikely as (1) benzodiazepines have low abuse liability following acute usage[26] and (2) once the akathisia was controlled, the patients did not ask for an additional injection.

Overall, the results of this study suggest that IV diazepam may be efficacious for the immediate relief of subjective distress of akathisia. For the patient who wants

immediate relief from the severe distress of akathisia, IV diazepam may be one of the choices. The choices are whether usual antiakathisia treatment described above is solely to be commenced or IV diazepam is also administered at the beginning of the usual treatment. The latter treatment can be used as a temporary measure until the appearance of the effect of the subsequent usual antiakathisia treatment. However, although severe side effects such as apnea did not appear in this study, the risks and benefits of the IV administration of diazepam must be cautiously weighed. IV diazepam may be considered for patients who require immediate relief, on the condition that they are fully informed of the risks and benefits, contraindications for IV diazepam are ruled out, and artificial ventilation and IV flumazenil are available.

This study was conducted as an open-label trial in a relatively small number of patients. Therefore, an appropriate, larger-scale, placebo-controlled study will be required to determine if IV diazepam is useful in providing rapid relief in severe cases of akathisia. In addition, the comparison between patients in the randomly assigned oral drug group and IV injection group at the beginning of akathisia treatment would be needed.

Drug names: biperiden (Akineton), diazepam (Valium and others), flumazenil (Romazicon), haloperidol (Haldol and others), propranolol (Inderal and others), risperidone (Risperdal).

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