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INTRAVENOUS BIPERIDEN IN AKATHISIA: AN OPEN PILOT STUDY

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ABSTRACT

Objective: Antipsychotic-induced akathisia can be distressing and unendurable for prolonged periods. It has been shown that intramuscular biperiden is a relatively rapid and effective treatment for akathisia. However, the intravenous administration of biperiden may provide a more rapid effect, although this remains to be definitively proven. *Method:* The subjects obtained for this study met the diagnostic criteria for schizophrenia as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The therapeutic effect of i.v. and i.m. biperiden was studied in an open clinical trial in twenty-three (12 male and 11 female) patients who developed antipsychotic-induced acute akathisia as defined by the research criteria of the DSM-IV. Following the development of akathisia, 5 mg of biperiden was intravenously injected in seventeen patients and intramuscularly in six patients. The therapeutic effect of biperiden on akathisia was clinically assessed by using the rating scale of Barnes. *Results:* Following i.v. administration on biperiden, the mean time to onset and maximum effect occurred 1.6 (*SD* = 1.9) and 9.2 minutes (*SD* = 6.0), respectively. Furthermore, at the time of maximal effect, akathisia was completely ameliorated in all patients. The side effects reported were mild and transient. Following i.m. administration, the mean time to onset and maximum effect were 30.5 (*SD* = 5.9) and 50 minutes (SD = 7.4), respectively. Thus, the time to maximal effect was significantly less (40 minutes) after i.v. compared to i.m. administration. *Conclusion:* These results suggest that i.v. administration of 5 mg of biperiden could be used to provide a rapid and effective treatment for patients with severe akathisia.

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Key Words: antipsychotic drug-induced, akathisia, biperiden, intravenous injection

INTRODUCTION

Akathisia is a common side effect produced by typical antipsychotic drugs [1-3], although the overall incidence of antipsychotic-induced akathisia has decreased due to the increased use of atypical antipsychotics [4-6]. However, typical antipsychotics are still used in many patients.

Generally, akathisia has two components: a subjective feeling of inner restlessness and objective restless movements [7]. Akathisia can be severely distressing to the patient [8]; thus, a rapid amelioration of akathisia would be desirable. However, the treatment of akathisia is sometimes delayed or not administered because akathisia can be: 1) difficult to diagnose [9, 10], 2) overlooked or ignored, and 3) misdiagnosed [9, 11-14]. For example, akathisia symptoms may be mistaken for agitation or anxiety, depression, or an exacerbation of psychosis [8, 15-18]. Unfortunately, when akathisia is misdiagnosed as an exacerbation of psychosis, the dose of the antipsychotic is increased, and the patient's condition worsens. Therefore, in ambiguous cases, differential diagnosis is necessary before treatment can be initiated. A positive response to anti-akathisia medications may prove helpful in differentiating the symptoms of akathisia from those related to other psychiatric disorders. Indeed, if the treatment completely eliminates akathisia, this allows for an appropriate diagnosis and treatment.

Several approaches that may be used to ameliorate akathisia include discontinuation of the drug, dosage reduction, or switching to a lower potency antipsychotic drug [19]. However, if the patient's illness does not allow any of the aforementioned options, anti-akathisia agents, such as -blockers, anticholinergic agents and benzodiazepines may be administered [17, 20]. The time until the appearance of a therapeutic effect with these treatments is of considerable importance. For example, akathisia may not be completely absent until several days to a week following a reduction in the dose of the antipsychotic drug or discontinuation [19]. In contrast, -blockers, which are believed to produce the most rapid effect among the orally administered agents, demonstrate efficacy in the treatment of akathisia within a several to forty-eight hours [20, 21]. Although the intravenous administration of diazepam [22] produces a rapid effect, it may not be useful in differentiating the agitation and restlessness in akathisia from anxiety in other psychiatric conditions.

One of the most rapid ways to treat akathisia is to administer the anticholinergic agent biperiden via the intramuscular (i.m.) route [16]. However, a more rapid relief from akathisia would be desirable, particularly in patients experiencing extreme distress. A treatment that provides more rapid relief would be better for ambiguous cases of akathisia, particularly for outpatients, as they cannot be released from the hospital until a definitive treatment plan is established. Therefore, intravenous (i.v.) biperiden may prove beneficial as it would theoretically produce a rapid relief of akathisia as well provide a rapid diagnostic treatment.

Ayd [23] and Medina [24] reported that there was no significant difference between the intravenous and intramuscular administration of biperiden in the

onset of effect in the treatment of antipsychotic-induced parkinsonism. However, other authors [25-27] have reported an immediate effect following the i.v. administration of 5 mg of biperiden against parkinsonian symptoms, with the maximum effect appearing within zero to five minutes after the injection. In patients with akathisia, it was reported that it took twenty to sixty minutes for the therapeutic effect occur following i.m. biperiden [16]. However, there have been very few reports describing the use of i.v. biperiden in the treatment of akathisia [17, 26-28].

This article reports the effect of i.v. and i.m. biperiden in the treatment of antipsychotic-induced acute akathisia in patients requiring rapid relief.

METHODS

The studies were carried out in an open clinical trial at Fukui Prefectural Mental Hospital between July 1998 and December 1999. The subjects obtained for this study met criteria for the diagnosis of schizophrenia as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [7] and were patients whom the author (H.S.) treated during the aforementioned period. The subjects consisted of twelve males and eleven females (outpatients or inpatients) and ranged in age from nineteen to sixty. The subjects were selected consecutively following the development of akathisia following the administration of antipsychotic medication. Furthermore, these were the patients who required that their restlessness be rapidly relieved. Patients with mild akathisia that did not require rapid relief were not included in the study, as well as patients with a history of or active indication of narrow angle glaucoma, cardiac arrhythmias, or prostatic hypertrophy. Antipsychotic-induced acute akathisia was defined according to the research criteria in Appendix B in DSM-IV. Seventeen patients between July 1998 and April 1999 received i.v. biperiden and other six patients received i.m. biperiden between April 1999 and December 1999. Following the development of antipsychotic-induced acute akathisia, 1 ml of a solution containing 5 mg of biperiden in a syringe was injected into the median cubital vein through a needle (21G 1.25 inch) over a period of two minutes in seventeen patients. This dose was chosen to allow comparison with the i.m. studies [11, 16], that also used a 5 mg dose of biperiden. All twenty-three subjects received biperiden injection within twenty-four hours of the appearance of akathisia. The severity of inner restlessness was rated by the author (H.S.), using the Barnes's akathisia scale [29]: 0 (absent), 1 (non-specific sense of inner restlessness), 2 (awareness of an inability to keep the legs still or complaints of inner restlessness specifically aggravated by being required to remain still), or 3 (awareness of an intense compulsion to move most of the time). The patients were asked about their subjective restlessness by the author every thirty seconds during and after the injection. The time to onset of effect was defined as the time the patient first acknowledged the amelioration of subjective restlessness, i.e., when the rating scale score was decreased by 1 point.

The time required to reach the maximum effect was defined as when the patient first acknowledged the complete disappearance of subjective restlessness, i.e., rating scale score of 0. Objective restless movements were not regarded as an index of the time effect of the treatment because as the intensity of the akathisia decreases with treatment, the objective restless movements may be less notable [19, 30], especially at the time of formal rating [31]. Thus, the appearance of objective restless movements becomes less correlated with the intensity of akathisia as the signs/symptoms abate with treatment. Blood pressure and heart rate were measured in all subjects before and after the injection. Furthermore, subjects were asked if they experienced the standard anticholinergic side effects known to occur after biperiden administration (e.g., drowsiness, confusion, dry mouth, abdominal discomfort, and visual disturbance), as well as side effects other than the aforementioned ones.

RESULTS

The mean time to the onset and maximum effect of the amelioration of akathisia following the i.v. and i.m. administration of biperiden are listed in Table 1. The mean time to onset of action in i.v. administration was significantly shorter than i.m. by twenty-eight minutes ($P < 0.05$, *t*-test) in this study. The mean time to maximum effect in i.v. was also significantly shorter than i.m. by 40 minutes ($P < 0.05$, *t*-test).

The complete suppression or amelioration of akathisia persisted for at least four hours in seventeen patients following i.v. administration of biperiden. Side effects were reported in six cases. The most commonly reported side effects following the i.v. biperiden were slight or mild confusion, drowsiness, dizziness, palpitations, and dry mouth. All of these abated within a few hours and did not have any serious clinical consequences. The blood pressure and heart rate of some patients was altered after the injection of biperiden (± 5 to 20 mm Hg systolic for blood pressure and ± 5 to 25 pulses/min), although these returned to pre-biperiden baseline values within a few hours and had no serious clinical effects.

Table 1.

Route of Administration	Mean Time to the Effect (minutes)	
	Onset	Maximum
I V (n = 17)	1,6 ± 1,9	9,2 ± 6,0
I M (n = 6)	30,5 ± 5,9	50,0 ± 7,3

IV: Intravenous administration of biperiden
IM: Intramuscular administration of biperiden
Each value represents the mean time ± *SD*

Table 2. Summary of Patient Demographics, Medication Regimens, Ratings of Akathisia and the Therapeutic Effects Produced by i.v. (Case 1–17) and i.m.(Case 18–23) Biperiden in Antipsychotic Drug-Induced Akathisia Patients

Case	Age	Sex	Administration before Injection(mg)	Ratings of Subjective Restlessness before Injection	Ratings before Injection Rigidity	Tremor	Time to Onset of Effect(m)	Time to Maximum Effect(m)	Side Effects
1	39	M	Risperidone (12)	2	0	0	1	5	drowsiness
2	26	F	Haloperidol (12)	2	1	1	1	5	–
3	25	M	Haloperidol (9) Zotepine (75)	3	0	0	0	0.5	–
4	33	F	Haloperidol (18)	2	1	1	3	15	confusion
5	25	F	Haloperidol (18)	2	0	1	3	12	drowsiness
6	50	M	Haloperidol (9)	2	2	2	2	4	–
7	60	M	Haloperidol (9)	3	0	0	1	11	–
8	35	M	Timiperone (9)	2	0	0	0	7	confusion dizziness
9	23	F	Haloperidol (12)	3	0	1	1	18	dry mouth palpitation
10	51	M	Haloperidol (2)						
11	54	M	Haloperidol (12)	3	0	0	8	20	Confusion
12	19	M	Risperidone (9)	3	2	2	2	10	–
			Haloperidol (3) Biperiden (6)	2	0	0	0	9	dizziness dry mouth

13	50	F	Haloperidol (20)	3	2	2	2	8	dizziness
14	44	F	Haloperidol (9) Biperiden (3)	2	0	0	1	4	
15	21	F	Haloperidol (10) Biperiden (2)	3	0	0	2	20	–
16	27	M	Haloperidol (18) Biperiden (6)	2	0	1	0	4	–
17	28	F	Risperidone (12)	3	0	0	0.5	4	–
18	58	M	Risperidone (3) Biperiden (3)	2	0	0	40	60	drowsiness
19	41	F	Zotepine (150) Biperiden (6) Trihexyphenydil (8)	2	0	0	10	20	–
20	21	F	Haloperidol (6)	3	0	1	30	60	–
21	41	M	Haloperidol (5) Biperiden (4)	3	0	0	18	40	–
22	52	M	Chlolpromazine (75) Biperiden (9)	2	0	0	50	70	–
23	28	F	Risperidone (6)	2	0	0	35	50	dry mouth

Following the i.m. administration of biperiden, akathisia was completely ameliorated for at least three hours in six patients. Two of the patients reported drowsiness and dry mouth, which were mild and transient.

The age, sex, and daily dosage of drugs, as well as ratings of subjective restlessness and extrapyramidal signs [32] before the injection, and side effects after the i.v. and i.m. administration of biperiden are summarized in Table 2.

Case Examples

Case 1

A thirty-nine-year-old man, with a thirteen-year history of schizophrenia, was admitted to the hospital with an exacerbation of his psychosis that resulted from his non-compliance to his medication regimen. The patient was given six mg p.o. of risperidone daily, and the following week, the dose was increased to 12 mg as the patient had not shown significant improvement. This treatment produced a gradual abatement in the hallucinations. However, three days after increasing the dose, he suddenly complained of discomfort of the trunk and legs. He said that he felt anxious and did not feel comfortable in any position in the bed and he walked about. Upon questioning, he acknowledged inner restlessness and the inability to remain still and stated that this was severely distressing to him. He showed no other extrapyramidal symptoms. Subsequently, the patient was given 5 mg i.v. of biperiden over a period of two minutes. One minute after the injection, he definitely acknowledged that his feeling of inner restless was beginning to abate. Five minutes after the injection, he acknowledged the complete disappearance of inner restlessness after objective restless movements had already disappeared, although he reported feeling slightly drowsy. His systolic and diastolic blood pressure were decreased by about 20 mm Hg and his pulse was decreased by fifteen minutes below pre-biperiden baseline. His drowsiness disappeared after one hour and his blood pressure and pulse rate returned to normal after two hours. The dose of risperidone was reduced from 12 mg to 6 mg and 9 mg of oral biperiden, t.i.d., was added to his daily medication regimen. Five hours after the biperiden injection, the patient reported a reappearance of his feeling of inner restlessness and that he was distressed to the point of asking for another injection. Subsequently, 5 mg of biperiden was given intravenously and his restlessness ceased five minutes later. The patient has remained free of restlessness following this treatment.

Case 2

A twenty-six-year-old woman came to the hospital with a relapse in her condition one year after being diagnosed with schizophrenia. Initially, she was given 6 mg p.o. of haloperidol daily and the dose was increased to 12 mg the following week. During the third week of treatment, she complained of insomnia and restlessness. In addition, she walked about in the night and shouted to relieve the distress produced by the feeling of restlessness. The next day, the patient received 5 mg of biperiden

intravenously and her restlessness ceased within five minutes. No significant side effects were reported. Subsequently, 9 mg p.o. of biperiden, t.i.d. and 2 mg p.o. of flunitrazepam before bedtime were added to her daily drug regimen. The following day after the i.v. administration of biperiden, she reported a return of restlessness. The intensity was milder than the day before and she did not require the i.v. administration of biperiden. Sixty mg p.o. of propranolol, t.i.d. was added and the dose of haloperidol was reduced to 6 mg. Two days later, her restlessness had completely disappeared and did not re-emerge.

DISCUSSION

Braude [19] reported that anticholinergics were more effective in treating antipsychotic-induced akathisia in patients with accompanying parkinsonism compared to patients without parkinsonism. However, anticholinergics in that report were administered orally. In contrast, i.v. and i.m. biperiden in the current study was effective in treating antipsychotic-induced akathisia in patients with or without parkinsonism. Thus, the therapeutic effects produced by parental administration might be different from those produced via the oral route.

In this study, there were wide differences among the twenty-three patients in the time required to reach the maximal effect following i.v. and i.m. biperiden. This wide difference in time to therapeutic effect following the administration of biperiden has been reported in antipsychotic-induced parkinsonism [25-27] as well. The explanation for the wide differences between patients in current study is unknown. These differences could be due to a number of pharmacokinetic and pharmacodynamic factors. For example, one factor that could explain the wide variation is differences in plasma levels and it may prove useful to measure biperiden levels in future studies.

Despite the wide differences between patients in the time effect, the results of this study suggest that i.v. biperiden produces a more rapid therapeutic effect than i.m. biperiden in akathisia. Based on the results, the i.v. administration of biperiden could be considered when patients require rapid relief from akathisia and have no contraindications for biperiden such as narrow angle glaucoma.

In this study, all patients that required rapid relief accepted the i.v. injection of biperiden without hesitation. They were cooperative, possibly because the distress in akathisia is ego-alien [11], and therefore they wanted relief. It took about ten to thirty seconds to obtain i.v. access in this study. It did not seem that specific skill was required in i.v. access. The reported side effects in this study were all slight or mild and transient. They had no significant clinical consequences. Consequently, it was considered that the therapeutic effect far surpassed the adverse effect, i.e., the risk/benefit ratio was acceptable. However, doses lower than 5 mg may be preferable for elderly patients, who are more sensitive to the side effects of biperiden. It should be pointed out that this study did not include patients with narrow angle glaucoma, cardiac arrhythmias, or prostatic hypertrophy. In addition, this study was

carried out in an open manner in a small number of patients. An appropriate, larger scale, placebo-controlled study will be required to determine if i.v. biperiden can be accepted for general use in the treatment of distressing cases of antipsychoti-induced akathisia.

It has been reported that 5 mg of i.m. biperiden can be used to differentiate and treat ambiguous cases of akathisia [16]. However, this study was not designed to differentiate ambiguous akathisia from other psychiatric conditions. A further study would be required to determine if i.v. biperiden can be successfully used in treating ambiguous cases of akathisia requiring rapid relief.

REFERENCES

1. Sachdev P. The epidemiology of drug-induced akathisia. *Schizophrenia Bulletin* 1995;21 (3):431–461.
2. Malhotra AK, Litman RE, Pickar D. Adverse effects of antipsychotic drugs. *Drug Safety* 1993;9 (6):429–36.
3. Casey DE. Motor and mental aspects of extrapyramidal syndromes. *International Clinical Psychopharmacology* 1995;10 (Suppl 3):105–14.
4. Dawkins K, Lieberman JA, Lebowitz BD, Hsiao JK. Antipsychotics: Past and future national institute of mental health division of services and intervention research workshop, July 14, 1998. *Schizophrenia Bulletin* 1999;25 (2):395–405.
5. Holloman LC, Marder SR. Management of acute extrapyramidal effects induced by antipsychotic drugs. *American Journal of Health System Pharmacy* 1997;54:2461–2477.
6. Umbricht D, Kane JM. Medical complications of new antipsychotic drugs. *Schizophrenia Bulletin* 1996;22 (3):475–483.
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders 4th ed.* Washington, D.C.: APA, 1994.
8. Kalinowsky LB. Appraisal of the "tranquilizers" and their influences on other somatic treatment in psychiatry. *American Journal of Psychiatry* 1958;115:294–300.
9. Ratey JJ, Salzman C. Recognizing and managing akathisia. *Hospital and Community Psychiatry* 1984;35 (10):975–977.
10. Van Putten T, Marder SR. Behavioral toxicity of antipsychotic drugs. *Journal of Clinical Psychiatry* 1987;48 (Suppl):13–9.
11. Van Putten T. The many faces of akathisia: *Comprehensive Psychiatry* 1975;16 (1):43–7.
12. Drake RE, Sederer LI. The adverse effects of intensive treatment of chronic schizophrenia. *Comprehensive Psychiatry* 1986;27 (4):313–26.
13. Weiden PJ, Mann JJ, Haas G, Mattson M, Frances A. Clinical nonrecognition of neuroleptic-induced movement disorders: A cautionary study. *American Journal of Psychiatry* 1987;144 (9):1148–53.
14. Kaplan HI, Sadock BJ. *Comprehensive textbook of psychiatry VI. 6 ed.* Baltimore: Williams & Wilkins, 1995.
15. Sachdev P, Loneragan C. The present status of akathisia. *Journal of Nervous and Mental Disease* 1991;179 (7):381–391.

16. Van Putten T, Mutalipassi LR, Malkin MD. Phenothiazine-induced decompensation. *Archives of General Psychiatry* 1974;30 (1):102–5.
17. Tonda ME, Guthrie SK. Treatment of acute neuroleptic-induced movement disorders. *Pharmacotherapy* 1994;14 (5):543–60.
18. Ayd FJJ. The present status of akathisia (Letter). *Journal of Nervous and Mental Disease* 1992;180 (3):208–209.
19. Braude WM, Barnes TR, Gore SM. Clinical characteristics of akathisia. A systematic investigation of acture psychiatric inpatient admissions. *British Journal of Psychiatry* 1983;143:139–50.
20. Blaisdell GD. Akathisia: A comprehensive review and treatment summary. *Pharmacopsychiatry* 1994;27:139–146.
21. Lipinski JF, Jr., Zubenko GS, Cohen BM, Barreira PJ. Propranolol in the treatment of neuroleptic-induced akathisia. *American Journal of Psychiatry* 1984;141 (3):412–415.
22. Gagrat D, Hamilton J, Belmaker RH. Intravenous diazepam in the treatment of neuroleptic-induced acute dystonia and akathisia. *American Journal of Psychiatry* 1978;135 (10):1232–1233.
23. Ayd FJ. Drug-induced extrapyramidal reactions: Their clinical manifestations and treatment with akineton. *Psychosomatics* 1960;1:2–8.
24. Medina C, Kramer MD, Kurland AA. Biperiden in the treatment of phenothiazine-induced extrapyramidal reactions. *JAMA* 1962;15:1127–1129.
25. Madalena JC. *Ensaios Preliminares com o biperideno Injetavel no Tratamento Neurodislepticas Induzidas por Drogas Neurolepticas.* Apresantado no IX Congresso Nacional de Neurologia, Psiquiatria e Higiene Mental. 1969, Rio: 6–11.
26. Kline NS, Mason BT, Winick L. Biperiden (Akineton): Effective prophylactic and therapeutic anti-parkinsonian agent. *Current Therapeutic Research, Clinical and Experimental* 1974;16 (8):838–843.
27. Eckmann F. Zur Behandlung neurileptisch bedingter grobmotorisch-extrapyramidaler Syndrome. *Ther d Gegenw* 1963;102:349–356.
28. Fleischhacker WW, Roth SD, Kane JM. The pharmacologic treatment of neuroleptic-induced akathisia. *Journal of Clinical Psychopharmacology* 1990;10 (1):12–21.
29. Barnes TRE. A rating scale for drug-induced akathisia. *British Journal of Psychiatry* 1989;154:672–676.
30. Van Putten T, Marder SR. Toward a more reliable diagnosis of akathisia [letter]. *Archives of General Psychiatry* 1986;43 (10):1015–1016.
31. Sachdev P. A rating scale for acute drug-induced akathisia: Development, reliability, and validity. *Biological Psychiatry* 1994;35:263–271.
32. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavia* 1970;212 (Suppl):11–19.

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