REVIEW

Current Topics in Neuroleptic-induced Extrapyramidal Symptoms in Japan

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Abstract. This article reviews current topics in neuroleptic-induced extrapyramidal symptoms in Japan, focusing especially on the clinical features of akathisia and dystonia. Akathisia is a common side effect associated with antipsychotic drugs. It is most commonly characterized by subjective inner restlessness and objective motor signs, especially in the lower extremities. The mechanisms underlying akathisia remain unclear and controversial; however, an increase in the activity of β-adrenergic systems relative to dopaminergic systems has been hypothesized, based on clinical therapeutic observations that β-blocking agents are effective in this condition. A Japanese version of the Barnes Akathisia Scale has recently been established and uses a standardized videotape method for its precise evaluation. Various acute and chronic manifestations of neuroleptic-induced dystonia have been reported in Japan, including blepharospasm, difficulty in opening the eye lids, torticollis, retrocollis, oculogyric crisis, and Pisa syndrome. This review also introduces several other topics related to drug-induced extrapyramidal symptoms in Japan. These include: 1) the Drug-Induced Extra-Pyramidal Symptoms Scale (DIEPSS), which has recently been established, 2) studies on the discontinuation of anticholinergic drugs, and 3) a summary of extrapyramidal symptoms induced by drugs other than neuroleptics. (Keio J Med 45 (2): 95-99, June 1996)

Key words: neuroleptics, akathisia, dystonia, extrapyramidal symptoms, DIEPSS

Introduction

Forty years have passed since neuroleptics were introduced into Japan in 1955. During these four decades, the treatment of psychiatric illnesses with these drugs has contributed considerably not only to the remission of the disease itself but to the facilitation of social rehabilitation in psychiatric patients. However, these drugs have not always been beneficial to psychiatric patients; some patients have not responded well to neuroleptics, and others have suffered from uncomfortable side effects such as extrapyramidal symptoms even at recommended therapeutic dosages. These symptoms include parkinsonism, dystonia, akathisia, and tardive dyskinesia (Fig 1). The present review describes current topics in neuroleptic-induced extrapyramidal symptoms in Japan, focusing especially on the clinical features of akathisia and dystonia.

Akathisia

Akathisia is a common side effect associated with antipsychotic drugs. Although it is difficult to define precisely, it most commonly comprises both subjective inner restlessness and objective motor signs, especially in the lower extremities. The prevalence of akathisia reported in Japan ranges from 4.5% to 46.0%. This condition has often caused clinical concern because: 1) it is a frequent cause of patient non-compliance with neuroleptic treatment, often resulting in the relapse of psychosis, 2) it sometimes induces anxiety, behavioral deterioration, and even suicide, and 3) it is considered to be an early predictive factor for tardive dyskinesia.

β-blockers in the treatment of akathisia

The mechanisms underlying the development of...
neuroleptic-induced akathisia remain unclear and controversial. However, an imbalance between central dopaminergic and β-adrenergic systems may be implicated in the pathophysiology of this condition. An increase in the activity of β-adrenergic systems relative to dopaminergic systems has been hypothesized, based on clinical therapeutic observations that β-blocking agents, such as propranolol, are effective in this condition. However, as far as we know, no β-blocking agents have been officially approved for use in the treatment of akathisia in any country. Previously reported double-blind studies of β-blocking agents in the treatment of akathisia have also, unfortunately, all had a small sample size. In Japan, a placebo-controlled double-blind phase II study of carteolol, a hydrophilic β-blocker, in the treatment of neuroleptic-induced akathisia has recently been conducted. A total of 107 psychiatric patients with akathisia were recruited, and the results showed that carteolol significantly decreased the symptoms of akathisia. A phase III double-blind placebo-controlled study of this agent is currently being performed.

Akathisia and iron status

It has been suggested in some studies that low levels of iron could be implicated in the pathophysiology of neuroleptic-induced akathisia. Horiguchi examined iron levels in 35 patients receiving neuroleptic drugs and found that patients exhibiting akathisia or dystonia had significantly lower serum iron concentrations than those without. Subsequently, the same author performed a trial of iron therapy in patients with neuroleptic-induced akathisia and reported a good response in three out of 5 patients. Fujikawa et al have also described 2 patients with restless legs syndrome who were treated successfully with iron therapy.

Barnes akathisia scale (Japanese version)

One of several rating scales for drug-induced akathisia, the Barnes Akathisia Scale, has recently been translated into Japanese and the reliability of its Japanese version has been established. Generalized kappa values for inter-rater reliability among eight trained raters were found to be higher than 0.68 for all items, and Cohen's kappa values for test-retest reliability when performed by 2 trained raters were higher than 0.88 for all items. In the course of this process, the importance of training raters prior to clinical evaluation and the usefulness of a standardized videotape method in their training were confirmed in this study. This scale has been used in the phase II and phase III placebo-controlled double-blind studies of carteolol in the treatment of neuroleptic-induced akathisia.

Tardive akathisia

Acute akathisia usually responds well to anticholinergic agents. However, these drugs are not generally effective in the late-onset type of this condition, tardive akathisia. The mechanisms underlying tardive akathisia are thought to be different from those of the acute type, and to be similar to those underlying tardive dyskinesia. More than 10 cases have been reported in Japan to date, since our first report of tardive akathisia in 1988. In contrast to the disappointing performance of treatment regimens for tardive dyskinesia, tardive akathisia seems to be reversible and a couple of successful treatment regimens for this condition have been reported. Nishikawa et al recommended clonidine therapy together with the discontinuation of anticholinergic drugs as an effective treatment, while Kuniyoshi et al reported that relatively low doses of clonazepam had beneficial effects in patients with tardive akathisia which could not be controlled by anti-parkinsonian drugs. Tanaka et al reported a patient with tardive akathisia and oculogyric crisis, in whom diazepam (15 mg/day) was effective in relieving both symptoms.

Dystonia

Dystonia is a syndrome involving hypertonicity of the muscles, and is manifested by stiffness, twisting, spasms, contraction, and persistent abnormal muscle positions. It can occur in the tongue, neck, extremities, and trunk. Various manifestations of neuroleptic-induced dystonia have been reported in Japan. These include blepharospasm, difficulty in opening the eye lids, tongue protrusion, torticollis, retrocollis, oculogyric crisis, and Pisa syndrome. A number of therapeutic trials for various dystonic manifestations have been reported in the Japanese literature.

Inada T and Yagi G: Extrapyramidal Symptoms in Japan
Blepharospasm

Fukuzako et al reported 3 patients with tardive dystonia involving blepharospasm.\(^{14,15}\) The symptoms were alleviated by trihexyphenidyl (12 mg/day) in 2, while reduction of the haloperidol dose was effective in the remaining patient.\(^{18,15}\) Mino et al reported that clonidine (0.15 mg/day) was effective in one patient whose dystonic symptoms did not respond to neuroleptic dose reduction (bromperidol 4 mg/day to 2 mg/day).\(^{16}\)

Difficulty in opening the eye lids

Difficulty in opening the eye lids is a rare side effect of neuroleptics which often develops together with blepharospasm. These symptoms have been often discussed in terms of their relationship to neuroleptic-induced Meige’s syndrome. Oomagari et al described seven psychiatric patients with difficulty in opening their eye lids induced by neuroleptics.\(^{17}\) Symptoms were transient and diminished after neuroleptic dose reduction in most cases. The authors considered the pathophysiology of this condition to be different from that of tardive dyskinesia. Tanaka et al described a patient who responded dramatically to diazepam (15 mg/day).\(^{13}\)

Pisa syndrome

Pisa syndrome is a dystonic reaction that appears in association with neuroleptic therapy and is considered to be a subtype of tardive dystonia. Suzuki et al reported a patient with this condition who was successfully treated by changing medication from haloperidol (18 mg/day) to pimozide (18 mg/day).\(^{18}\)

Meige’s syndrome

Kimura et al reported the case of a schizophrenic mother and daughter who both exhibited Meige’s syndrome after neuroleptic therapy, and suggested that genetic factors could be involved in the vulnerability to neuroleptic-induced movement disorders.\(^{19}\) Trihexyphenidyl was effective in relieving the daughter’s symptoms. Clonazepam has also been reported to be effective in a few cases of Meige’s syndrome induced by neuroleptics.\(^{20,21}\)

Tardive dystonia

Tardive dystonia is a late-onset neuroleptic-induced movement disorder and its prevalence in Japan has been estimated as 0.5–2.1% in psychiatric patients receiving neuroleptics.\(^{22,23}\) Although the mechanisms underlying tardive dystonia have previously been considered to be similar to those speculated for tardive dyskinesia, it is now widely thought that tardive dystonia is a separate entity rather than a subtype or variant of tardive dyskinesia, due to differences in its manifestation, response to treatment, and epidemiological findings. Although the condition has been considered refractory in most cases,\(^{10}\) dantrolene sodium has been reported effective in several cases.\(^{24–26}\) Koga et al first reported 3 cases of tardive dystonia in Japan,\(^{27}\) which satisfied the criteria proposed by Burke et al.\(^{28}\) They reported that clonidine had some effect in all these patients. Harada et al subsequently followed the clinical courses of 44 patients with tardive dystonia and reported that symptoms improved in 6 of 9 patients who received clonidine.\(^{29}\)

Other Topics

Drug-induced extrapyramidal symptoms scale (DIEPSS)

Although the Simpson & Angus extrapyramidal symptoms (EPS) scale\(^{30}\) has been widely used in western countries, it has rarely been used in studies conducted in Japan. Therefore, there is no accumulated EPS data evaluated using this scale. The establishment of a standardized rating scale in Japan has been strongly advocated in order to evaluate neuroleptic-induced extrapyramidal symptoms precisely. As a result, the DIEPSS has been designed and its reliability has recently been established.\(^{10}\) DIEPSS consists of eight individual parameters and one global assessment. The individual parameters are: gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia and dyskinesia. Although this scale was originally written in English so that international comparisons could be performed easily, an exact Japanese translation is added under each original English sentence for the convenience of Japanese raters. The severity of each item is graded from 0 (normal) to 4 (severe), and each category has clearly defined anchor points.

The degree of severity of extrapyramidal side effects, as well as the antipsychotic effects, has been given greater weight than ever in evaluating the value of new antipsychotic drugs. The DIEPSS has become a standard rating scale for the evaluation of extrapyramidal side effects in Japan, and is being used in several double-blind studies of new antipsychotic drugs now being developed in Japan (Table 1). The DIEPSS was also used in the clinical study of carteolol in the treatment of neuroleptic-induced akathisia (phase III) and of rolipram in the treatment of tardive dyskinesia (phase II).

Studies on the discontinuation of anticholinergic drugs

One of the prominent characteristics of psychopharmacologic strategies in Japan is the fact that the vast majority of patients receive prophylactic anticholinergic drugs. These are usually prescribed in combination with
neuroleptics from the beginning of antipsychotic therapy to prevent extrapyramidal side effects. However, this prophylactic concomitant use of anticholinergic drugs has sometimes been criticized as being unnecessary. Nishimatsu et al attempted to withdraw anticholinergic drugs in a total of 100 patients who showed neither akathisia nor parkinsonism and observed that seventy eight (78%) did not develop any extrapyramidal symptoms.\(^3\) In another study, Takeuchi et al discontinued anticholinergic drugs in 48 schizophrenic patients receiving these agents in combination with neuroleptics.\(^3\) They reported that only nine (19%) of these patients required readministration due to the development or exacerbation of extrapyramidal symptoms. These studies suggest that anticholinergic drugs are unnecessary in approximately 80% of patients receiving them in combination with neuroleptics in Japan.

**Extrapyramidal symptoms induced by drugs other than neuroleptics**

A number of drugs other than neuroleptics have been reported to cause extrapyramidal symptoms. The agents implicated in Japanese reports are shown in Table 2.\(^3\) Flunarizine has been reported to lead to extrapyramidal symptoms, such as parkinsonism and akathisia, in approximately 17–61% of Japanese recipients.\(^2\) Extrapyramidal symptoms have often been reported to develop due to the concurrent use of two or more kinds of benzamide derivative, such as metoclopramide, tiapride, and sulpiride.\(^6\) Because the indications for these drugs are different, these situations are apt to occur in patients who attend more than one clinic.

**References**

11. Nishikawa T, Koga I, Kamata K, Uchida Y, Tanaka M: Treat-

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**Table 1** New Antipsychotic Drugs Being Developed in Japan

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPC-14597*</td>
<td>Phase III</td>
</tr>
<tr>
<td>Serquel (ICI-204,636)*</td>
<td>Phase III</td>
</tr>
<tr>
<td>Olanzapine (LY-170,053)*</td>
<td>Phase III</td>
</tr>
<tr>
<td>Sertrindole (S-1,991)*</td>
<td>Phase III</td>
</tr>
<tr>
<td>SM-9018</td>
<td>Phase III</td>
</tr>
<tr>
<td>AD-5423</td>
<td>Phase II</td>
</tr>
<tr>
<td>Ziprasidone (CP-88,059)</td>
<td>Phase II</td>
</tr>
<tr>
<td>NE-100</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

* Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) has been used for the evaluation of neuroleptic-induced extrapyramidal symptoms in Phase III clinical double-blind studies of the drugs denoted by an asterisk.

**Table 2** Drugs Which Have Been Reported to Induce Extrapyramidal Symptoms

<table>
<thead>
<tr>
<th>Groups</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substituted Benzamides</td>
<td>metoclopramide, tiapride, sulpiride*</td>
</tr>
<tr>
<td>H2 Antagonists</td>
<td>cimetidine, ranitidine</td>
</tr>
<tr>
<td>Anti-cancer Drugs</td>
<td>fluorouracil, tegafur, carbomafur</td>
</tr>
<tr>
<td>Other Gastrointestinal Drugs</td>
<td>domperidone, cisapride, eleboride malate</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>diltiazem, flunarizine, cinnarine</td>
</tr>
<tr>
<td>Other Anti-hypertensive Drugs</td>
<td>reserpine*, α-methyldopa</td>
</tr>
<tr>
<td>Mood Stabilizers</td>
<td>lithium, carbamazepine</td>
</tr>
</tbody>
</table>

Drugs listed in this table are principally used as those other than antipsychotic drugs, except for those denoted by an asterisk. Data are adapted from Yagi et al.\(^3\)


