Sulpiride in Meige's Syndrome: Possible Role of Glutamate

Sang-Am Lee¹, Jin-Soo Kim¹, Jae-Hoon Ahn¹ and Kyoung-Gyu Choi¹

Sulpiride, a selective antagonist for adenylyl cyclase-independent dopamine receptors, was administrated to 25 patients with blepharospasm and oromandibular dystonia (Meige's syndrome). Of the 25, 7 patients (28%) exhibited marked and lasting improvement with sulpiride and 12 patients (48%) showed mild or transient improvement. This favorable therapeutic response to sulpiride suggests that striatal glutamate underactivity may play a role in the pathophysiology of Meige's syndrome as a primary or secondary defect.

Key Words: Meige's syndrome, sulpiride, glutamate

The pathophysiology of Meige's syndrome (MS) has not been established. Marsden (1976) proposed that MS is an adult form of idiopathic torsion dystonia such as spasmodic torticollis and dystonic writer's cramp. Although the pharmacological response of MS is inconsistent in several reports (Marsden et al. 1983; Nutt et al. 1984) certain pharmacological studies indicate that central dopaminergic preponderance (Tolosa and Lai 1979; Casey 1980) or central cholinergic hyperfunction (Tanner 1982) are possible biochemical bases for this syndrome.

The possibility of striatal dopaminergic preponderance has been suggested by several authors because of favorable responses to apomorphine (Tolosa and Lai 1979; Casey 1980) perphenazine (Casey 1980), haloperidol (Tolosa and Lai 1979) and tetrabenazine (Jankovic and Ford 1983). However, these agents cannot antagonise one subpopulation of dopamine (DA) receptors selectively. Sulpiride, a substituted benzamide, is a potent and selective antagonist for adenylyl cyclase-independent DA receptors (Jenner and Marsden 1981). We therefore studied the therapeutic effects of sulpiride in patients afflicted with MS.

Patients and Methods

MS was diagnosed clinically in 25 patients (9 men and 16 women), aged 33 to 66 years (average, 55). The mean duration of illness was 4.6 years (ranging from 6 months to 20 years) and the mean age of onset was 48 years (ranging from 31 to 65). Fourteen patients presented blepharospasm alone, while 11 patients experienced the complete syndrome. Of those with the complete syndrome, one case had an involuntary spasm extending to the neck muscles and an other patient had an essential tremor (Table 1).

All patients were evaluated with medical, ophthalmological and neurologic examinations. Their medical histories and records were carefully reviewed to exclude patients on antipsychotic medication. Brain CT scans performed on 7 patients revealed no gross abnormalities. Brainstem-evoked responses and routine cerebrospinal fluid (CSF) studies were done on 6 hospitalized patients, and the results were within normal limits.

The degree of disability was assessed on a functional scale. Particular attention was paid to the patient's ability to work, go outdoors alone, read and watch television. The percentage of time during a typical day when the eyes were closed by blepharospasm was calculated and the patients were categorized as severe (eyes shut for over 80% of the day: n=14), moderate (eyes shut for 30-80% of the day: n=9) and mild (eyes shut for 10-30% of the day: n=9).
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n=2 (Elston and Russell 1985).

All patients underwent a pharmacotherapeutic trial with 400 to 600mg sulpiride per day for at least 4 weeks. The response to therapy was evaluated by the patients' reports, by direct observation, by at least one

of the authors and by reports of family members. The results were rated as mild or transient (less than three months) or marked and lasting (more than three months) (Cramer and Otto 1986).

RESULTS

Of the 25 patients, seven (28%) produced marked and lasting improvement with sulpiride, and 12 (48%) showed mild or transient improvement (Table 2). Of the 7 patients with marked and lasting improvement, 3 (patients 5, 7 and 11) stopped taking the medication because of nearly complete improvement. But the symptoms gradually recurred two weeks after withdrawal of the medication. Improvement with sulpiride had no correlation with the degree of disability of the disease, age of onset, sex, duration of illness, or type of disease, and so was unpredictable.

Of the 25 cases, six patients showed side effects attributable to sulpiride (Table 3). Drowsiness was the principal complaint in 3 cases, while lactation, acute dystonia and weight gain were noticed in 3 other cases. The medication was discontinued on the patient who experienced lactation.

DISCUSSION

Sulpiride is a selective agent which interacts with

Table 3. Side effects of sulpiride

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>6 (3, 12, 24)</td>
</tr>
<tr>
<td>Acute dystonia</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Lactation</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Numbers in parenthesis indicate patient number (Table 1).

Table 2. Results of treatment with sulpiride on Meige's syndrome

<table>
<thead>
<tr>
<th>Disability of disease</th>
<th>n</th>
<th>Marked and lasting (more than 3 months)</th>
<th>Transient or mild (less than 3 months)</th>
<th>No Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>2</td>
<td>2 (4, 13)</td>
<td>2 (4, 13)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>9</td>
<td>3 (2, 5, 23)</td>
<td>4 (10, 17, 20, 25)</td>
<td>2 (12, 15)</td>
</tr>
<tr>
<td>Severe</td>
<td>14</td>
<td>4 (7, 11, 18, 22)</td>
<td>6 (1, 8, 9, 19, 21, 24)</td>
<td>4 (3, 6, 14, 16)</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>7 (28%)</td>
<td>12 (48%)</td>
<td>6 (24%)</td>
</tr>
</tbody>
</table>

Numbers in parenthesis indicate patient number (Table 1).
cerebral DA receptors, but, apparently it has virtually no affinity for other neuronal systems in the brain. Sulpiride also appears to interact only with one subpopulation of DA receptors, that which acts independently of adenylate cyclase. It appears that those receptors for which sulpiride shows the highest affinity lie on the terminals of the corticostriatal glutamate fibers. Sulpiride enhances glutamate release from the terminals of the corticostriatal glutamatergic fibers by blocking the presynaptic DA receptor of that fiber (Jenner and Marsden 1981; Kim et al. 1983).

The present study showed that sulpiride treatment in MS produced marked and lasting improvement in 28% of the patients and transient or mild improvement in 48% of the cases. This favorable therapeutic response with sulpiride in MS could suggest that the underactivity of glutamate in the neostriatum plays a role in the pathophysiology of MS as a primary or secondary defect. The corticostriatal glutamatergic input exerts an excitatory effect on gabaminergic functions in the neostriatum (Wood et al. 1979: Giorgi and Meek 1984). The underactivity of glutamate in the neostriatum, therefore, could result in decreased gabaminergic function. That may be supported by a marked decrease in pallidal r-amino butyric acid (GABA) concentration in the brain of a patient with postencephalitic dystonia (Fahn 1976) and decreased CSF GABA levels in patients with MS (Neophytides et al. 1978). Enhanced glutamate release by sulpiride increases GABA activity in the neostriatum, and this probably attenuates the symptoms of MS.

Pharmacologic studies have suggested a state of dopaminergic and/or cholinergic hyperfunction in MS (Tolosa and Lai 1979; Casey 1980; Tanner et al. 1982). Further, the observed prominent cholinergic enhancement separates MS pharmacologically from tardive dyskinesia (Tolosa and Lai 1979; Stahl et al. 1982). Tolosa and Lai (1979) have suggested a striatal dopaminergic preponderance, since both apomorphine and haloperidol attenuated the dystonic spasms. They hypothesized a disturbance of the striatonigral gabaminergic cells, resulting in a disinhibition of nigral DA neurons and in the postulated dopaminergic striatal preponderance. Casey (1980) stated that the prompt and dramatic aggregating effect of carbidopa/levodopa in MS is consistent with a striatal dopaminergic preponderance, and could be due to an idiopathic form of striatal DA receptor hypersensitivity. In contrast to Tolosa and Lai and Casey, Tanner et al. (1982), in acute studies, found that intramuscular scopolamine improved their patients. Also the action was reversed by subsequent IM phystostigmine. In a subsequent chronic oral study using benztprine or trihexyphenidyl for some weeks or months, they found that 12 of 13 patients improved. They have, therefore, suggested that "Acetylcholine (ACh) plays a role in the pathophysiology of MS."

From a functional point of view, cholinergic interneurons receive an excitatory input from the cerebral cortex and an inhibitory input from the substantia nigra, through glutamate and DA, as their neurotransmitters (KerKerian and Nieoullon 1983). Reciprocal presynaptic interactions have been evidenced between these two afferent pathways (Nieoullon et al. 1978; Schwaroz et al. 1978; Roberts and Anderson 1979; Roberts et al. 1982). Ach was shown to inhibit glutamate transmission directly via presynaptic ACh receptor located on glutamate nerve terminals (KerKerian and Nieoullon 1983). Also ACh has been shown to facilitate striatal DA release by means of an ACh presynaptic receptor on DA nerve terminals (Greenamyre et al. 1985), this results in an inhibition of glutamate release via DA receptors on corticostriatal glutamate fibers.

The underactivity of glutamate could be interpreted as a primary or secondary event. If increased DA activity in the brain is a primary abnormality in this condition, then decreased activity of the glutamate neurons may occur as a compensatory mechanism. However, it is difficult to explain cholinergic hyperfunction in MS because the nigrostriatal dopaminergic input was shown to inhibit cholinergic intrastriatal interneurons (Bernardi et al. 1978; Siggine 1978). Also there is no convincing direct evidence for central dopaminergic hyperactivity in MS. In this case, it is equally possible that there is normal function in the DA system in MS, but hypoactivity of the glutamate system instead. Glutamatergic hypofunction, therefore, could be secondary to cholinergic hyperfunction or the primary defect seen in Huntington's chorea (Giorgiuef et al. 1977; Kim et al. 1980) and schizophrenia (Kim et al. 1980, 1983; Kim and Kornhuber 1982). However, it must be said that this thesis is probably a simplification, because the brain consists not only of isolated neuronal groups, but also of interconnected circuits involving different transmitters which are regulated by various control mechanisms. Moreover, MS is possibly a heterogeneous disorder because MS displays inconsistent pharmacological properties.

In conclusion, the desirable therapeutic effect of sulpiride in MS suggests that striatal glutamate underactivity may play an important role in the pathophysiology of MS as a primary defect seen in the degenerative change of the corticostriatal fibers,
or a secondary defect to cholinergic hyperfunction.

REFERENCES


Kim JS, Claus D, Kornhuber HH: Cerebral glutamate, neuroleptic drugs and schizophrenia: Increase of cerebrospinal fluid glutamate levels and decrease of striate body glutamate levels following sulpiride treatment in rat. *Eur Neurol* 22:367-370, 1983


