View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

ORIGINAL ARTICLE

Short-term Sulpiride Treatment of Children and Adolescents With Tourette Syndrome or Chronic Tic Disorder

Che-Sheng Ho,[1,2] Hui-Ju Chen,[1,3] Nan-Chang Chiu,[1,2] Ein-Yiao Shen,[1,4] Hung-Chi Lue[3]*

Background/Purpose: Tourette syndrome (TS) is characterized by motor and vocal tics, and its diagnosis is based on clinical criteria. Dopamine-blocking neuroleptics are regarded as the most effective drugs for the treatment of TS. Sulpiride is a selective dopamine D2 antagonist. However, only one study with a large number of patients has reported the effect of treatment of TS with sulpiride. The purpose of this study was to evaluate prospectively the effect of sulpiride treatment of children and adolescents with TS or chronic tic disorder.

Methods: The inclusion criteria were patients who fulfilled the diagnosis of TS or chronic tic disorder, and who had not received previous treatment. The severity of TS was assessed by the Yale Global Tic Severity Score (YGTSS) every 2 weeks for a total of 6 weeks. The patients started treatment with low-dose sulpiride according to their age on the first visit. The adverse effects of sulpiride were evaluated by subjective complaints from the patients themselves or their parents. The change in scores between each assessment point was analyzed by repeated measures one-way analysis of variance, with SPSS version 12.0 software.

Results: One hundred and eighty-nine patients were enrolled. Their average age was 8.0 ± 2.5 years (range, 3–15 years). Most patients were male ($n = 165$, 87.3%). Six weeks' treatment significantly improved motor tics ($p < 0.05$), vocal tics ($p < 0.05$) and total YGTSS ($p < 0.05$). The most commonly encountered adverse effect was sedation ($n = 31$, 16.4%).

Conclusion: Sulpiride is effective for short-term treatment of children and adolescents with TS or chronic tic disorder, and has few adverse effects. [*J Formos Med Assoc* 2009;108(10):788–793]

Key Words: sulpiride, tics, Tourette syndrome

Tourette syndrome (TS) is a chronic neuropsychiatric disorder that is characterized by motor and vocal tics. Diagnosis is based solely on clinical criteria. The prevalence of this syndrome is estimated to be between one and 10 per 1000 children and adolescents.[1] A variety of neurotransmitters have been implicated in the pathophysiology of TS, and a variety of pharmacological agents have been used for the treatment of patients with tics, including agonists and/or antagonists for dopamine, serotonin, norepinephrine, acetylcholine, γ-aminobutyric acid and opioid systems.[1,2] Traditional antipsychotics are still the mainstay of pharmacological treatment for TS, and haloperidol remains the most frequently prescribed medication for the disorder.[3] However, many patients experience intolerable adverse effects, including sedation, extrapyramidal symptoms, akathisia, and

©2009 Elsevier & Formosan Medical Association

[1]Department of Pediatrics, Mackay Memorial Hospital, [2]Mackay Medicine, Nursing and Management College, Taipei, [3]Department of Pediatrics, Saint Mary's Hospital Luodong, I-Lan, and [4]Graduate Institute of Acupuncture Science, China Medical University, Taichung, Taiwan.

Received: March 13, 2009
Revised: March 18, 2009
Accepted: March 31, 2009

***Correspondence to:** Dr Hui-Ju Chen, Department of Pediatrics, Saint Mary's Hospital Luodong, 160 Chung-Chen South Road, Luodong, I-Lan 26546, Taiwan.
E-mail: hjuchen0623@yahoo.com.tw

weight gain, which lead to two-thirds of patients who show improvement with treatment choosing to discontinue haloperidol.[4]

Of the other several potential therapeutic antipsychotics, dopamine-blocking neuroleptics seem to be the most effective drugs for the treatment of TS, although the role of dopamine in tics is still controversial. Sulpiride is a selective dopamine D2 antagonist with antipsychotic and antidepressant activity, and is also cost-effective. In a retrospective study in 1990, Robertson et al reported a 59% reduction in severity of TS in 63 patients treated with sulpiride.[5] The mean age of the patients was 29.3 years (range, 10–68 years) and only 10 of them were treated with sulpiride as a first-line agent. In the sulpiride responders, who included adults and children, the most commonly prescribed daily dose was 400 mg. To date, this is believed to be the only study with a relatively large number of patients.

We conducted an open-label study to assess prospectively the potential effect of a lower dose of sulpiride in children and adolescents with TS or chronic tic disorder.

Patients and Methods

We recruited children and adolescents with TS or chronic tic disorder who agreed to participate in the study, and were not taking any tic-suppressing medication. Informed consent was obtained from all the parents. TS or chronic tic disorder was diagnosed by two experienced pediatric neurologists (CS Ho and NC Chiu) at our outpatient clinic between January 2005 and December 2007, on the basis of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2000). The severity of TS was assessed by the Yale Global Tic Severity Score (YGTSS).[6] This scale consists of ratings for motor and vocal tics, in terms of number, frequency, intensity, complexity, and interference. The YGTSS has excellent interactive reliability.[6] We rated the scores at the first clinic visit as the baseline scores and then every 2 weeks, for a total of 6 weeks of follow-up. The clinical rating at each visit was recorded by the same clinicians to avoid personal bias in severity evaluation.

All the patients started with low-dose sulpiride according to their age at the first visit. For patients aged >7 years, the initial dose was 100 mg twice daily (half a 200-mg tablet). For patients aged ≤ 7 years, the initial dose was 67 mg twice daily (a third of a 200-mg tablet). The dose was increased every 2 weeks (50–100 mg/day) if the YGTSS did not show improvement and no intolerable adverse effects were experienced. The adverse effects of sulpiride were evaluated by subjective complaint from the patients themselves or their parents, by questionnaire. At the end of the study, the average sulpiride dose in patients ≤ 7 years of age was 156 mg/day, and in patients >7 years of age, it was 205 mg/day.

The baseline scores, including motor tic, vocal tic and total scores, were compared with the scores at weeks 2, 4 and 6. The serial score changes were analyzed by one-way analysis of variance (ANOVA), with group as a between-subject factor, to compare symptom severity at the various assessment points, measured with SPSS version 12.0 software (SPSS Inc., Chicago, IL, USA).

Results

Of the 198 patients recruited, 189 (171 children and 18 adolescents) completed the trial. Five patients were lost to follow-up and four were withdrawn from the study because they received more than one antipsychotic agent in addition to sulpiride. The mean age was 8.0 ± 2.5 years (range, 3–15 years). There were 165 male and 24 female patients. One hundred and thirteen patients fulfilled the criteria of TS, and another 71 had chronic motor tic disorder and five had chronic vocal tic disorder. At baseline, the average motor tic score evaluated by YGTSS was 12.71 ± 0.24; the average vocal tic score was 6.59 ± 0.46; and the mean total YGTSS was 32.72 ± 0.89. At the end of the study (week 6), the average motor tic score was 6.45 ± 0.59; the average vocal tic score

was 2.38 ± 0.47; and the average total YGTSS was 13.36 ± 1.43. This represented a mean reduction of 49% in motor tic score, 64% in vocal tic score, and 59% in total YGTSS. Vocal tics were more responsive to sulpiride than were motor tics. All except three patients had a reduced severity score at week 6 compared with baseline. Two of the exceptions underwent examination at school and one had a common cold during therapy. In the one-way ANOVA, a significant drug effect was found between each assessment point, except between weeks 2 and 4 (Tables 1–3). There was a significant reduction in motor tic scores (Table 1) and total YGTSS (Table 3) between baseline and weeks 2, 4 and 6; however, vocal scores were only significantly reduced between baseline and week 6 (Table 2). There was no significant reduction in scores between weeks 2 and 4 in motor tics, vocal tics and total YGTSS. Mean age, baseline mean score, and week 6 mean score for TS, chronic motor tic and chronic vocal tic patients are outlined in Table 4. Compared with baseline YGTSS, significant improvement after 6 weeks of treatment was seen for motor tics ($p < 0.05$), vocal tics ($p < 0.05$) and total YGTSS ($p < 0.05$; Figure).

The mean initial treatment dose was 176 mg/day and the mean treatment dose at the end of the study was 190 mg/day, which was not a significant

Table 1. Comparison of motor tic scores between baseline and weeks 2, 4 and 6

Score (A) (mean ± SD)	Score (B)	Mean difference (A – B)	95% CI	*p*
Baseline (12.71 ± 0.24)	Week 2	2.22	0.87 to 3.58	0.000*
	Week 4	2.71	1.15 to 4.28	0.000*
	Week 6	6.26	4.68 to 7.84	0.000*
Week 2 (10.49 ± 0.39)	Baseline	–2.22	–3.58 to –0.87	0.000*
	Week 4	0.49	–1.24 to 2.22	0.890
	Week 6	4.04	2.29 to 5.79	0.000*
Week 4 (10.00 ± 0.56)	Baseline	–2.71	–4.28 to –1.15	0.000*
	Week 2	–0.49	–2.22 to 1.24	0.890
	Week 6	3.55	1.63 to 5.46	0.000*
Week 6 (6.45 ± 0.59)	Baseline	–6.26	–7.84 to –4.68	0.000*
	Week 2	–4.04	–5.79 to –2.29	0.000*
	Week 4	–3.55	–5.46 to –1.63	0.000*

**p < 0.05, one-way analysis of variance. SD = standard deviation; CI = confidence interval.*

Table 2. Comparison of vocal tic scores between baseline and weeks 2, 4 and 6

Score (A) (mean ± SD)	Score (B)	Mean difference (A – B)	95% CI	*p*
Baseline (6.59 ± 0.46)	Week 2	0.75	–1.21 to 2.71	0.762
	Week 4	1.47	–0.79 to 3.74	0.345
	Week 6	4.22	1.93 to 6.51	0.000*
Week 2 (5.84 ± 0.56)	Baseline	–0.75	–2.71 to 1.21	0.762
	Week 4	0.72	–1.79 to 3.23	0.886
	Week 6	3.47	0.93 to 6.00	0.002*
Week 4 (5.12 ± 0.65)	Baseline	–1.47	–3.74 to 0.79	0.345
	Week 2	–0.72	–3.23 to 1.79	0.886
	Week 6	2.75	–3.18 to 5.52	0.054
Week 6 (2.38 ± 0.47)	Baseline	–4.22	–6.51 to –1.93	0.000*
	Week 2	–3.47	–6.00 to –0.93	0.002*
	Week 4	–2.75	–5.52 to 3.18	0.054

**p < 0.05, one-way analysis of variance. SD = standard deviation; CI = confidence interval.*

Table 3. Comparison of total YGTSS scores between baseline and weeks 2, 4 and 6

Score (A) (mean ± SD)	Score (B)	Mean difference (A – B)	95% CI	*p*
Baseline (32.72 ± 0.89)	Week 2	5.15	0.93 to 9.38	0.009*
	Week 4	8.19	3.31 to 13.08	0.000*
	Week 6	19.37	14.43 to 24.30	0.000*
Week 2 (27.57 ± 1.16)	Baseline	–5.15	–9.38 to –0.93	0.009*
	Week 4	3.04	–2.37 to 8.45	0.479
	Week 6	14.21	8.75 to 19.67	0.000*
Week 4 (24.53 ± 1.64)	Baseline	–8.19	–13.08 to –3.31	0.000*
	Week 2	–3.04	–8.45 to 2.37	0.479
	Week 6	11.17	5.18 to 17.16	0.000*
Weez 6 (13.36 ± 1.43)	Baseline	–19.37	–24.30 to –14.43	0.000*
	Week 2	–14.21	–19.67 to –8.75	0.000*
	Week 4	–11.17	–17.16 to –5.18	0.000*

**p < 0.05, one-way analysis of variance. YGTSS = Yale Global Tic Severity Score; SD = standard deviation; CI = confidence interval.*

Table 4. Mean age, baseline mean score and week 6 mean score of three groups of patients

	Tourette's syndrome (*n* = 113)	Chronic motor tic disorder (*n* = 71)	Chronic vocal tic disorder (*n* = 5)
Mean age (yr)	8.18 ± 0.25	7.91 ± 0.29	6 ± 0.71
Baseline mean score	37.26 ± 1.08	26.41 ± 1.25	23.75 ± 3.09
Week 6 mean score	14.49 ± 1.65	11.26 ± 3.15	17 ± 0.21

change. The most common adverse effect with sulpiride treatment was sedation early in the trial (*n* = 31, 16.4%). However, in none of the patients was sedation severe enough to interfere with daily activity or school performance. The second most common adverse effect was increased appetite (*n* = 14, 7.4%). One patient reported a body weight gain of 2 kg after 6 weeks of treatment. The adverse effects are listed in Table 5. None of our patients experienced extrapyramidal symptoms.

Discussion

TS is characterized by multiple motor tics plus one or more vocal (phonic) tics, which characteristically wax and wane. TS is now recognized to be associated with a wide variety of associated behaviors and psychopathology.[7] The most commonly prescribed medications for motor and vocal tics have been the dopamine antagonists. The most successful agents in this group are haloperidol, pimozide, sulpiride and tiapride, whereas risperidone and ziprasidone are two atypical neuroleptics with proven tic-suppressing efficacy.[5,8–13] Haloperidol, a butyrophenone derivative, is primarily a dopamine D2 receptor blocker.[14] It is one of the most widely prescribed agents used in treating TS in the United States, Canada, United Kingdom, Europe, Australasia and the Far East.[7] However, it has been suggested that haloperidol produces unacceptable adverse effects in 84% of patients, and therefore, only a minority of 20–30% of TS patients continue treatment for extended periods.[15]

Atypical neuroleptics are believed to have a low risk of tardive dyskinesia and acute extrapyramidal reactions. As a result of potential QT changes, baseline and follow-up electrocardiography is recommended for risperidone, ziprasidone and pimozide. It is also essential for the prescribing clinician to be familiar with potential

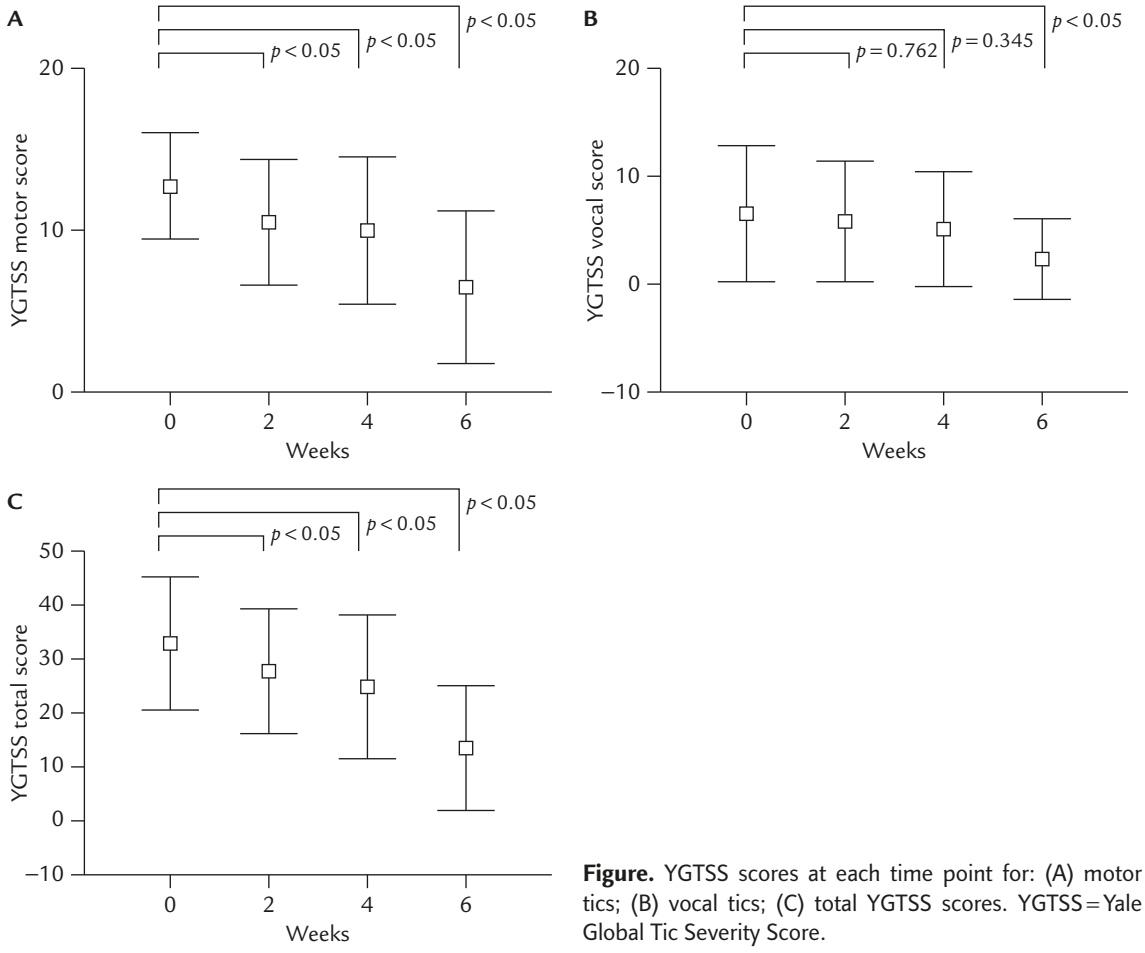

Figure. YGTSS scores at each time point for: (A) motor tics; (B) vocal tics; (C) total YGTSS scores. YGTSS = Yale Global Tic Severity Score.

Table 5. Adverse effects of sulpiride treatment in 189 patients

Adverse effect	Patients, *n* (%)
None	152 (80.4)
Sedation	31 (16.4)
Increased appetite	14 (7.4)
Headache	4 (2.1)
Depression	2 (1.1)
Abdominal pain	2 (1.1)
Dizziness	1 (0.5)
Impaired concentration	1 (0.5)

cytochrome-P450-related drug reactions, because fatal interactions have arisen with pimozide and erythromycin-related antibiotics.[16]

The substituted benzamides, selective D2 antagonists, have become popular for the treatment of motor and vocal tics, and produce less extrapyramidal side effects and tardive dyskinesia.[7] The most widely documented benzamide for treatment of TS is sulpiride, first used by Yvonneau and Bezard in 1970.[17] In the only double-blind trial with this drug, George et al undertook a 14-week placebo-controlled, crossover study of fluvoxamine versus sulpiride, followed by single-blind combined treatment in 11 patients with comorbid TS and obsessive–compulsive disorder (OCD). Sulpiride monotherapy greatly reduced tics and non-significantly improved OCD symptoms.[10] Robertson et al managed 63 of 114 (55%) TS patients (mean age, 29.3 years) with sulpiride, and found that beneficial effects occurred in 59% of patients. Positive effects were: decreased motor and vocal tics; OCD; aggression; echophenomena and tension; and improved mood. The dose of sulpiride in their study commenced at 200 mg/day and increased to a limit of 1 g/day.[5]

In our study, most patients were male, with a male to female ratio of 7:1, which is much higher

than in previous studies, and implies that there is a male predominance in TS of unknown cause. With short-term sulpiride treatment in children with TS or chronic tic disorder, we found significant symptom reduction, which supports the findings in previous studies. As far as we are aware, our study was the second largest trial to date of sulpiride treatment in patients with TS, and was the largest study to show a good response to sulpiride in children and adolescents with TS or chronic tic disorder.

The most common adverse effect of sulpiride is mild sedation, which is tolerable for all patients and often disappears at 1 or 2 weeks after treatment. No extrapyramidal symptoms were found with the low dose of sulpiride used in this study. There was no tardive dyskinesia in the study of Robertson et al,[5] which further supports our conclusion that sulpiride is a more acceptable choice than haloperidol. The limitation of our study is that most of our patients had disease of mild to moderate severity according to the YGTSS scale, and only a few patients had severe symptoms at initial presentation. This probably resulted from the younger patient age in our study than in previous studies. We could not conclude that sulpiride was effective in severe TS. However, early intervention and treatment of tics are important because long-standing symptoms may impair a patient's interpersonal relationships, academic performance, or social activities.[18] Further studies are necessary to assess the effect of sulpiride treatment in patients with severe TS.

In conclusion, sulpiride is a good short-term treatment choice for mild to moderate TS or chronic tic disorder in children and adolescents. Low-dose sulpiride is effective for treatment of TS or chronic tic disorder and has few adverse effects.

References

1. Singer HS. Tourette's syndrome: from behaviour to biology. *Lancet Neurol* 2005;4:149–59.
2. Jankovic J. Tourette's syndrome. *N Engl J Med* 2001;345: 1184–92.
3. Chappell PB, Scahill LD, Leckman JF. Future therapies of Tourette syndrome. *Neurol Clin North Am* 1997;15: 429–50.
4. Shapiro AK, Shapiro E, Eisenkraft GJ. Treatment of Gilles de la Tourette syndrome with clonidine and neuroleptics. *Arch Gen Psychiatry* 1983;40:1235–40.
5. Robertson MM, Schnieden V, Lees AJ. Management of Gilles de la Tourette syndrome using sulpiride. *Clin Neuropharmacol* 1990;13:229–35.
6. Leckman JF, Riddle MA, Hardin MT. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tics severity. *J Am Acad Child Adolesc Psychiatry* 1989;28: 566–73.
7. Robertson MM. Tourette syndrome, associated conditions and the complexities of treatment. *Brain* 2000;123:425–62.
8. Eggers C, Rothenberger A, Berghaus U. Clinical and neurobiological findings in children suffering from tic disease following treatment with tiapride. *Eur Arch Psychiatry Neurol Sci* 1988;237:223–9.
9. Sallee FR, Nesbitt L, Jackson C, et al. Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. *Am J Psychiatry* 1997;154:1057–62.
10. George MS, Trimble MR, Robertson MM. Fluvoxamine and sulpiride in comorbid obsessive–compulsive disorder and Gilles de la Tourette syndrome. *Hum Psychopharmacol* 1993;8:327–34.
11. Sallee FR, Kurlan R, Goetz CG, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry* 2000; 39:292–9.
12. Bruggeman R, van der Linden C, Buitelaar JK, et al. Risperidone versus pimozide in Tourette's disorder: a comparative double-blind parallel-group study. *J Clin Psychiatry* 2001;62:50–6.
13. Scahill L, Leckman JF, Schultz RT, et al. A placebo-controlled trial of risperidone in Tourette syndrome. *Neurology* 2003; 60:1130–5.
14. Messiha FS. Biochemical pharmacology of Gilles de la Tourette's syndrome. *Neurosci Biobehav Rev* 1988;12: 295–305.
15. Chappell PB, Leckman JF, Riddle MA. The pharmacologic treatment of tic disorders. *Child Adolesc Psychiatr Clin N Am* 1995;4:197–216.
16. Leckman JF. Tourette's syndrome. *Lancet* 2002;360: 1577–86.
17. Yvonneau M, Bezard P. Apropos of a case of Gilles de la Tourette's disease blocked by sulpiride. Psycho-biological study. *Encephale* 1970;59:439–59.
18. Jankovic J. Tourette's syndrome. *N Engl J Med* 2001;345: 1184–92.