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Long-Term Tolerability of Escitalopram in Korean Adolescents

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Objectives : We investigated the long-term tolerability of escitalopram in Korean adolescents.

Methods : The subjects were 37 adolescents, who had been diagnosed with depressive disorder in accordance to DSM-IV. Clinical effectiveness was assessed by Clinical Global Impression-Improvement (CGI-I) scale at the final follow-up visit. Tolerability was assessed through a medical record of the reason for discontinuation of escitalopram and documented adverse events.

Results : The mean duration of treatment was 78.1±89.5 days, and the mean dosage was 10.0±4.4mg/day. Out of the total 37 patients, two (5%) patients sustained use of escitalopram. Twelve patients (32.4%) discontinued use of escitalopram due to target symptom remission, and 23 patients (61.9%) due to insufficient efficacy. Six patients (16.2%) had at least one documented adverse event. However, no suicidal ideation or self-injurious behavior was reported. Significant differences in clinical symptom improvement efficacy were seen between the patients who were receiving escitalopram for less than 8 weeks (4.3%, 1/13) and those for more than 8 weeks (92.9%, 13/14). There was no significant difference between the tolerability of monotherapy compared to the concomitant use group.

Conclusion : The results of this study suggest that long-term use of escitalopram may result in superior efficacy than short-term use, and is tolerable in Korean adolescents with depression.

KEY WORDS : Adolescents · Depression · Escitalopram · Tolerability.

Introduction

The essential features of a major depressive episode are depressed mood and loss of interest or pleasure in nearly all activities for both the pediatric and adult population. However, adolescents with depression have greater impulsivity, irritability, more reckless behavior, and fewer neurovegetative symptoms (e.g., psychomotor retardation, low energy) than do adults with depression.[1-6] In adolescents, major depressive episodes are frequently associated with attention-deficit hyperactivity disorders, anxiety disorders, disruptive behavior disorders, substance-related disorders, and eating disorders[2]; and the median depressive episode length is 7 to 9 months with considerable risk for relapse.[1,7,8] Like depression in adults, adolescent depression is associated with prominent social and functional impairment.[1] Academic performance and functioning in family, school, and peer relationships are affected, and the risk of suicide is higher.[1,2] Furthermore, depression in adolescents frequently continues into adulthood, resulting in considerable morbidity and mortality.[9]

Escitalopram is the active S-enantiomer of the racemic citalopram, which acts as a specific competitive inhibitor of the membrane transporter of serotonin.[10,11] Moreover, escitalopram has been found to be more than twice as potent as citalopram and is the most selective agent in its class.[12] Escitalopram has no or very little affinity for other receptors such as the 5-HT_{1A}, 5-HT_2, dopamine D_1, and D_2 receptors.[10,11] Until 2009, only fluoxetine was approved by the US Food and Drug Administration (FDA) for acute and maintenance treatment of pediatric depression, in patients 8 to 18 years of age.[13] Escitalopram was approved by the FDA for acute and maintenance treatment of depression in adolescents 12 to 17 years of age.[14] We found two prospective randomized placebo controlled tri-

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als (RCTs) of escitalopram use in child and adolescent depression.[15,16] In one study conducted by Wagner et al., 268 subjects with depression (12-17-year-old adolescents), responded favorably to escitalopram in a post-hoc analysis.[16] In another RCT by Emslie et al., 312 adolescents with depression were randomized to receive either 10 to 20mg of escitalopram daily or placebo for 8 weeks.[15] They reported that use of escitalopram led to a greater reduction in Children's Depression Rating Scales-Revised (CDRS-R) scores.[15] In both RCTs, there was no difference between escitalopram and the placebo group in the discontinuation rate due to adverse effects, which was approximately 1.5-2.6%.[15,16] In a 16-week double-blind extension of the 8-week trial by Emslie et al.[15] Findling et al. observed a statistically significant CDRS-R reduction in the escitalopram group compared to the placebo group.[17] However, the discontinuation rate due to adverse events in the escitalopram group (5.2%) was significantly higher compared to the placebo group (0.8%) in the 16-week extension study.[17]

The adverse events reported in escitalopram trials in the pediatric population have been mostly mild to moderate.[18] And adult data suggest that escitalopram is safe and tolerable in most cases.[19] But SSRI-induced agitation and suicidality are still controversial and have led to the black-box warning issued by the FDA. A meta-analysis of short-term placebo-controlled trials of antidepressant drugs in children and adolescents showed an increased risk of suicidality during the first few months of antidepressant treatment compared to placebo.[20]

Although there has been an increase in the use of SSRIs for adolescent depression and tolerability is an important issue in SSRI use, particularly in the adolescent population, there are insufficient data on the long-term use of escitalopram in the adolescent population. To evaluate the tolerability of escitalopram in Korean adolescents, we examined the long-term use of escitalopram through retrospective review of medical records.

Methods

1. Subjects

The medical records from 2007 to 2008 of the Child and Adolescent Outpatient Clinic at SMG-SNU Boramae Medical Center were examined retrospectively. We identified 37 adolescent (13 to 18 years of age) outpatients diagnosed with a depressive disorder who were receiving escitalopram. Diagnoses were made by the treating psychiatrist and confirmed by a board-certified psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision.[21]

2. Data collection

Patient data collected from the medical record were evaluated for clinical information regarding the safety and tolerability of escitalopram. Target symptom for escitalopram was assessed through retrospective review of the charts. Its effectiveness was assessed through a review of self-reported target symptom improvement at the last follow-up visit. Board-certified Psychiatrist evaluated whether patients have improved or not, based on comment of patient or caregiver and clinician's impression of improvement through medical records. The clinician's impression of improvement in a patient's symptomatology was consistently recorded. Tolerability was assessed through a review of the reason for discontinuation of escitalopram and documented adverse events. The study protocol was approved by the institutional review board at SMG-SNU Boramae Medical Center (IRB No. 06-2009-3).

3. Data analysis

All statistical analyses were conducted using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Demographic data were analyzed by descriptive statistics and frequency analyses. Depending on the results of normality tests, the Mann-Whitney test or an analysis of variance was used to compare continuous variables. Fisher's exact test and the chi-square test were used to analyze categorical variables. All tests were 2-tailed, and a p value under 0.05 was considered statistically significant.

Results

1. Subject demographic and clinical data

The study included 16 males (43.2%) and 21 females (56.8%). The mean age was 15.8±1.7 years, and the age range was 13-18 years (Table 1). A total of 36 subjects were diagnosed with depressive disorder (97.3%), 1 patient was diagnosed with dysthymia (2.7%). 25 patients (67.6%) had a comorbidity including the following: attention-deficit hyperactivity disorder (18.9%), anxiety disorder (18.9%), pervasive developmental disorder (10.8%), mental retardation (5.4%), adjustment disorder (5.4%), obsessive-compulsive disorder (5.4%), and tic disorder (2.7%). The mean dosage was 10.0±4.4mg/day; 11 patients (29.7%) were taking 5mg/day of escitalopram; 18 patients (48.6%) were taking 10mg/day; 5 patients (13.5%) were taking 15mg/day; and 3 patients (8.1%) were taking 20mg/day. The mean duration of treatment was 78.1± 89.5 days (range, 7-396 days): 15 patients (40.5%) were treat-

Table 1. Demographic and clinical characteristics

	Subjects (N=37)
Sex, N (%)	
Male	16 (43.2)
Female	21 (56.8)
Age, years	
Mean (SD)	15.8 (1.7)
Range	13-18
Diagnosis, N (%)	
Unipolar depression	36 (97.3)
Dysthymia	1 (2.7)
Comorbidity, N (%)	
None	12 (32.4)
Attention-deficit hyperactivity disorder	7 (18.9)
Anxiety disorder	7 (18.9)
Pervasive developmental disorder	4 (10.8)
Mental retardation	2 (5.4)
Adjustment disorder	2 (5.4)
Obsessive-compulsive disorder	2 (5.4)
Tic disorder	1 (2.7)
Mean IQ (N, SD, range)	
Verbal IQ	94.9 (26, 19.3, 51-132)
Performance IQ	96.1 (26, 19.3, 51-134)
Full scale IQ	93.4 (28, 19.4, 49-136)
Dosage of escitalopram, mg/day	
Mean (SD)	10.0 (4.4)
Range	5-20
Duration of escitalopram, days	
Mean (SD)	78.1 (89.5)
Range	7-396
Side effects of escitalopram, N (%)	
None	31 (83.8)
Insomnia	1 (2.7)
Somnolence	1 (2.7)
Fatigue	1 (2.7)
Dizziness	1 (2.7)
Tremor	1 (2.7)
Restlessness	1 (2.7)
Concomitant medication, N (%)	
None	18 (48.6)
Antipsychotics	8 (21.6)
Anxiolytics	5 (13.5)
Other antidepressants	4 (10.8)
Methylphenidate	3 (8.1)
Mood stabilizer	2 (5.4)

SD : standard deviation, IQ : intelligence quotient

ed for less than 30 days (17.7±6.8 days): 8 patients (21.7%) were treated for 30-56 days (42.0±9.2 days): and 14 patients (37.8%) were treated for more than 56 days (166.3±101.7 days).

Each patient had one or more target symptoms for escitalopram (Table 2). The most frequent target symptoms were agitation (27.2%), depressed mood (27.2%), impulsivity (18.9%), and social withdrawal (16.2%). At the time of this study, only two patients continued use of escitalopram, and 35 out of 37 patients had discontinued escotalopram. Twelve patients (32.4%) stopped escitalopram due to target symptom remission, and 23 patients (61.9%) stopped its use due to insufficient efficacy or side effects. Patients reported symptom improvement in the domains of depressed mood, concentration, impulsivity, irritability, negative thought content, academic function, and social relationships.

Table 2. Frequency of concomitant symptoms

	Frequency of symptoms* N (%)
Depressed mood only	10 (27.2)
Social withdrawal	6 (16.2)
Lack of concentration	5 (13.5)
Anergia	3 (8.1)
Somatization	2 (5.4)
Impulsivity	7 (18.9)
Anger	5 (13.5)
Irritability	3 (8.1)
Suicidality	1 (2.7)
Agitation	10 (27.2)
Obsessive-compulsive behavior	2 (5.4)
Panic attack	1 (2.7)

* : Each patient can have more than one target symptom

In the total patient sample, 6 of the 37 subjects (16.2%) had at least one documented adverse event. Adverse events according to escitalopram dosage was as below; adverse event occurred in 18.2% (2 cases; insomnia, restlessness) of the 11 patients treated with 5mg/day, 11.1% (2 cases; fatigue, tremor) of the 18 patients treated with 10mg/day, 20% (1 case; dizziness) of the 5 patients treated with 15mg/day and 33.3% (1 case; somnolence) of the 3 patients treated with 20mg/day. One male patient treated with 15mg/day (aged 14) discontinued escitalopram administration due to admission to another hospital after 133 days of treatment. Suicide-related problems and self-injurious behavior were not reported.

2. Subjects who were receiving escitalopram for more than 8 weeks

When we compared patients who were on escitalopram for less than 8 weeks (mean duration of escitalopram use=27.4±12.5 days; 4.3%, 1/23) to those who were on escitalopram for more than 8 weeks (mean duration of use=161.4±99.4 days; 92.9%, 13/14), there was a statistically significant difference between the percentage of patients reporting improvement (χ^2=29.0, df=1, p<.01). Significant difference in the mean es-

citalopram dosage were seen between the patients who were on escitalopram for less than 8 weeks (mean dosage of escitalopram=8.3±3.2mg/day, p<.01) and those on escitalopram for more than 8 weeks (mean dosage of escitalopram= 12.9±4.7mg/day). The comparison between patients treated with escitalopram for less than 8 weeks and longer than 8 weeks are presented in Table 3. There was no significant difference in reported adverse events between two groups.

3. A comparison between the monotherapy and concomitant use groups

Eighteen of the 37 subjects received escitalopram monotherapy. The mean dosage was 9.2±3.5mg/day, and the mean duration was 59.1±60.2 days for patients on monotherapy. Nineteen patients were administered escitalopram with concomitant medications. In this group, the mean dose was 10.8±5.1mg/day, and the mean duration of treatment was 96.0±109.0 days. In the concomitant use group, 3 patients (15.8%) were taking stimulant medications. Other concomitant medications included antipsychotics (N=8, 42.1%), anxiolytics (N=5, 26.3%), other antidepressants (N=4, 21.1%) and mood stabilizers (N=2, 10.5%). In the escitalopram monotherapy group, 5 patients reported subjective improvement (27.8%), and 13 patients reported no improvement (72.2%). In the concomitant use group, 9 patients reported subjective improvement (42.1%), and 10 patients reported no improvement (57.9%). Escitalopram monotherapy was tolerable in most cases, with one patient (1/18, 5.6%) complaining of insomnia (Table 4). In 5 of the 19 patients treated with concomitant medications (26.3%), the reported adverse events during esci-

Table 3. Comparison between escitalopram use for less than 8 weeks and more than 8 weeks

Escitalopram use	<8 weeks (N=23)	>8 weeks (N=14)	p
Sex, N (%)			
Male	8 (34.8)	8 (57.1)	.305
Female	15 (65.2)	6 (42.9)	
Age, years			
Mean (SD)	15.7 (1.8)	16.1 (1.6)	.528
Duration of escitalopram, days			
Mean (SD) 27.4 (12.5)		161.4 (99.4)	<.01
Dosage of escitalopram, mg/day			
Mean (SD) 8.3 (3.2)		12.9 (4.7)	<.01
Response rate, N (%)			
Improved	1 (4.3)	13 (92.9)	<.01
Drug adverse events, N (%)	3 (13.0)	3 (21.4)	.653

Table 4. Comparison between monotherapy and polypharmacy

	Escitalopram monotherapy (N=18)	Escitalopram polypharmacy (N=19)	p
Sex, N (%)			
Male	6 (33.3)	10 (52.6)	.325*
Female	12 (66.7)	9 (47.4)	
Age, years			
Mean (SD)	15.6 (1.9)	16.1 (1.5)	.499†
Range	13-18	13-18	
Dosage of escitalopram, mg/day			
Mean (SD)	9.2 (3.5)	10.8 (5.1)	.443†
Range	5-15	5-20	
Duration of escitalopram, days			
Mean (SD)	59.1 (60.2)	96.0 (109.0)	.358†
Range	14-223	7-396	
Response, N (%)			.313*
Improved	5 (27.8)	9 (42.1)	
Not improved	13 (72.2)	10 (57.9)	
Drug adverse events, N (%)	1 (5.6)	5 (26.3)	.180*

* : Fisher's exact test, † : Mann-Whitney test

talopram administration were tremor (N=1, 5.3%), dizziness (N=1, 5.3%), somnolence (N=1, 5.3%), restlessness (N=1, 5.3%) and fatigue (N=1, 5.3%). However, there was no statistically significant difference between the monotherapy group and the concomitant use group.

Discussion

In this study, we retrospectively examined 37 adolescents with depression who were using escitalopram. In a prospective open-label study for fluoxetine, children and adolescents most frequently showed depressed mood (99.4%; 167/168), irritability (97%; 163/168), and impaired school performance (91.7%; 154/168) at baseline.[22] In our study, the most frequent target symptom was depressed mood because almost all of patients (97.3%) were diagnosed as depressive disorder. Twenty seven patients (72.8%) had concomitant target symptoms. The common concomitant symptoms were agitation (N=10, 27.2%), impulsivity (N=7, 18.9%), and social withdrawal (N=6, 16.2%). In a previous study of symptomatic expression in adolescent depression, the most frequent symptoms were depressed mood (94.9%; 535/564), irritability (66.1%; 373/564), social withdrawal (56.2%; 317/564), and psychomotor agitation (25.7%; 145/564).[5] Agitation was similar but social withdrawal was different from symptom frequency in previous study.

Medication dosing in most of the previous studies has been conducted based on extrapolations from the adult population.[23] In an open-label trial of escitalopram in children and adolescents with social anxiety disorder, 12 patients (60%; 12/20) were receiving 10mg/day of escitalopram, 4 (20%; 4/20) were receiving 15mg/day, and 4 (20%; 4/20) were receiving 20mg/day. The mean daily dosage of escitalopram was 12.7±2.1mg/day and response rate of escitalopram was 65% in previous study.[24] In our study, the mean daily dosage of escitalopram was 10.0±4.4mg/day and response rate of escitalopram was 37.4%.

Lower mean dosage or variable duration of escitalopram use in this study could be the reason for the lower response rate. So we compared patients according to duration of escitalopram use. The mean dosage of patients who administrated escitalopram more than 8 weeks was 12.9±4.7mg/day and was similar with previous study.[24] The response rate of patients who administrated escitalopram more than 8 weeks was superior than previous study (92.9% vs 65%).[24]

Twelve patients (32.4%) stopped escitalopram administration due to target symptom remission, and 23 patients (61.9%) stopped due to insufficient efficacy. Two patients (2/37) continued escitalopram treatment. Overall, 40% of the patients showed improvement. Moreover, when we compared patients who were on escitalopram for less than 8 weeks and those who were on escitalopram for longer than 8 weeks, there was a statistically significant difference between the rates of patients reporting improvement. All but one patient who used escitalopram for longer than 8 weeks reported improvement, whereas only one patient reported improvement for those who used it for less than 8 weeks. The mean duration of treatment for patients who discontinued due to no response was 27 days, suggesting that half of the patients who do not experience efficacy discontinue before one month. These results are similar or somewhat lower than other studies investigating the efficacy of escitalopram in children and adolescents. Our results are within the range of previous reports; however, they are limited because we did not have a placebo arm.

Our study demonstrated that escitalopram was generally well tolerated. In our study, adolescents using escitalopram experienced insomnia (N=1, 2.7%), somnolence (N=1, 2.7%), fatigue (N=1, 2.7%), dizziness (N=1, 2.7%), tremor (N=1, 2.7%), and restlessness (N=1, 2.7%). In a previous study, adolescents using escitalopram experienced insomnia (3.9%), influenza-like symptoms (3.9%), diarrhea (2%), nausea (2%), and abdominal pain (2%).[15] It is possible that not all adverse events were documented or reported unless they were of serious nature. In our study, serious adverse events, such as self-injurious behavior and suicidal attempts, were not reported, but there was one case of hospitalization. One patient reported restlessness, which may possibly put them at risk for future suicidal behavior or a switch to mania.[25] Previously, intentional self-injurious behaviors were reported for one patient on escitalopram compared to two placebo-treated subjects.[16] In another study, four patients in the escitalopram group experienced serious adverse events (2.6%; 4/155).[15]

We compared escitalopram use alone to its use in combination with other medications. It was previously suggested that there may be an increased risk of adverse drug reactions and drug interactions.[12] Accordingly, one adverse event (insomnia) was reported in the monotherapy group, while five adverse events (somnolence, fatigue, dizziness, tremor, restlessness) were reported in the concomitant use group in the present study. However, the rate of adverse events did not significantly differ between the two groups, suggesting that there is no significant difference between the tolerability of escitalopram monotherapy compared to combined use with other medications. Overall, the reported rates of side effects differ widely across the literature, which may be the result of different measures being used to evaluate side effects in dif-

ferent studies and the lack of standardized instruments.[25)]

Several limitations in our study need to be addressed. First, this study was evaluated by retrospective medical record with no randomization and no control group was included in the study design. The retrospective design of the study did not allow for other medications to be held constant. It is possible that some of the improvements in symptom severity may not be attributable solely to escitalopram. At the same time, it is possible that some of the side effects reported in our results could have been due to other medications. Despite these limitations, our study suggests that escitalopram may be safe and tolerable in Korean adolescents with depression. The results of this study also suggest that escitalopram may improve depressive symptoms in some adolescents. Although the findings of this study must be viewed in light of its limitations, it adds to the preliminary clinical data regarding the Korean adolescent patient population.

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