

Tipepidine in children with attention deficit/hyperactivity disorder: a 4-week, open-label, preliminary study

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Background: Tipepidine (3-[di-2-thienylmethylene]-1-methylpiperidine) has been used solely as a nonnarcotic antitussive in Japan since 1959. The safety of tipepidine in children and adults has already been established. It is reported that tipepidine inhibits G-protein-coupled inwardly rectifying potassium (GIRK)-channel currents. The inhibition of GIRK channels by tipepidine is expected to modulate the level of monoamines in the brain. We put forward the hypothesis that tipepidine can improve attention deficit/hyperactivity disorder (ADHD) symptoms by modulating monoaminergic neurotransmission through the inhibition of GIRK channels. The purpose of this open-label trial was to confirm whether treatment with tipepidine can improve symptoms in pediatric patients with ADHD.

Subjects and methods: This was a 4-week, open-label, proof-of-efficacy pilot study for pediatric subjects with ADHD. Ten pediatric ADHD subjects (70% male; mean age, 9.9 years; combined [inattentive and hyperactive/impulsive] subtype, n=7; inattentive subtype, n=3; hyperimpulsive subtype, n=0) received tipepidine hibenazate taken orally at 30 mg/day for 4 weeks. All subjects were assessed using the ADHD Rating Scale IV (ADHD-RS), Japanese version, and the Das-Naglieri Cognitive Assessment System (DN-CAS), Japanese version.

Results: A comparison of baseline scores and 4-week end-point scores showed that all the ADHD-RS scores (total scores, hyperimpulsive subscores, and inattentive subscores) improved significantly ($P<0.001$). Furthermore, a comparison of baseline DN-CAS total scores and 4-week end-point scores showed a mild trend of improvement ($P=0.093$). Tipepidine was well tolerated, with no patients discontinuing medication because of side effects.

Conclusion: Our pilot study suggests that tipepidine therapy may prove to be an effective alternative treatment for pediatric patients with ADHD. Nonetheless, more detailed randomized, double-blind trials are needed to confirm tipepidine's efficacy.

Keywords: attention deficit/hyperactivity disorder, tipepidine, GIRK channel, pediatric, anti-tussive, nucleus accumbens

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a common chronic psychiatric disorder, characterized by a pattern of developmentally inappropriate inattention, motor restlessness, and impulsivity, which affects between 3% and 7% of school-age children.¹ Prospective follow-up studies found that approximately 50% of children with ADHD show symptoms that continue into adulthood, and when left untreated are associated with substance abuse, depression, unemployment, and criminal offenses.^{2,3}

Clinical guidelines on the pharmacological treatment of ADHD recommend psychostimulants (eg, methylphenidate, dexamphetamine, mixed amphetamine salts,

lisdexamphetamine) and selective norepinephrine-reuptake inhibitors, such as atomoxetine.⁴ Psychostimulants are known to increase synaptic dopamine concentrations through inhibition of the dopamine transporter, a mechanism that facilitates dopamine reuptake into presynaptic neurons.⁵ Selective norepinephrine-reuptake inhibitors increase extracellular levels of norepinephrine and dopamine in the prefrontal cortex.⁶ This accumulating evidence suggests that behavioral problems associated with ADHD may be related to cognitive dysfunction and early disturbances in dopaminergic innervation of basal ganglia and the frontal lobe.⁷ Genetic and molecular studies of ADHD also demonstrate an association between this disease and dopamine-related genes.^{7–12} However, psychostimulants induce a variety of side effects, including anorexia, headaches, stomach aches, insomnia, pyrexia, and tics.¹³ Moreover, the frequency of suicidal ideation was greater among atomoxetine-treated patients compared with placebo groups.¹⁴ These results highlight the need to identify new therapies for ADHD, particularly treatment with fewer side effects than currently available drugs.

Tipepidine (3-[di-2-thienylmethylene]-1-methylpiperidine) has been used as a nonnarcotic antitussive in Japan since 1959. The safety of tipepidine in children and adults has already been established. Furthermore, suicide-related side effects have not been documented for tipepidine. It is reported that tipepidine inhibits G-protein-coupled inwardly rectifying potassium (GIRK)-channel currents.¹⁵ The activation of the GIRK channels causes membrane hyperpolarization through potassium efflux. The inhibition of GIRK channels by tipepidine is expected to modulate the level of monoamines in the brain, since GIRK channels are coupled with G-protein-coupled receptors, including 5-hydroxytryptamine (5-HT)_{1A}, adrenaline α_2 and dopamine D₂ receptors.¹⁵ Using *in vivo* microdialysis, Kawaura et al demonstrated that tipepidine increases the levels of 5-HT and catecholamines, including dopamine, in the prefrontal cortex of rats.¹⁶ Furthermore, Fujieda et al¹⁷ showed that tipepidine could attenuate the hyperactivity induced in methamphetamine-treated mice (an ADHD model) by modulating these monoamine systems. Given these results, we put forward the hypothesis that tipepidine can improve ADHD symptoms by modulating monoaminergic neurotransmission through the inhibition of GIRK channels coupled with monoamine receptors in the brain. The purpose of this open trial was to confirm whether treatment with tipepidine could improve symptoms in pediatric patients with ADHD.

Subjects and methods

Ethics statement

The ethics committee of Chiba University Graduate School of Medicine approved the study protocol (G24061), and all subjects provided written informed consent for participation in the study. We registered this trial on the official database of clinical research (ClinicalTrials.gov) on April 16, 2013 (NCT01835093).¹⁸

Study design and subjects

This was a 4-week, open-label, proof-of-efficacy pilot study for pediatric subjects with ADHD. The baseline demographic, clinical, and treatment characteristics of ADHD are shown in Table 1. All subjects received tipepidine hibenzate tablets. Tipepidine was taken orally at 30 mg/day (10 mg after breakfast, 10 mg after supper, and 10 mg before bedtime), for 4 weeks. Ten pediatric subjects with ADHD were recruited from Chiba University Hospital outpatients. All subjects were diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV criteria for ADHD,¹⁹ and were classified into three subtypes: combined (inattentive and hyperactive/impulsive), n=7; inattentive, n=3; and hyperimpulsive, n=0. Seven boys and three girls participated in this study. Seven subjects had received some drugs before entering the trial, namely methylphenidate (18–54 mg/day, n=2), atomoxetine (75 mg/day, n=1), aripiprazole (15 mg/day, n=1),

Table 1 Baseline demographics and clinical and treatment characteristics of ADHD subjects

Age (years \pm SD)	9.9 \pm 2.2
Sex (male/female)	7/3
Race (% Japanese)	100
Height (cm \pm SD)	140.5 \pm 15.5
Weight (kg \pm SD)	38.6 \pm 17.3
Tipepidine hibenzate dosage (mg/kg/day \pm SD)	1.288 \pm 0.349
ADHD subtypes (combined/inattentive/hyperimpulsive)	7/3/0
WISC-III/IV full IQ score \pm SD	87.4 \pm 13.3
Comorbidity (n)	4
Learning disorder	2
Tic disorder	1
Learning disorder and tic disorder	1
Pharmacotherapy (n)	7
Methylphenidate	2
Atomoxetine	1
Aripiprazole	1
Methylphenidate and atomoxetine	1
Atomoxetine and aripiprazole	1
Methylphenidate and risperidone	1
Naive	3

Note: Reported values are means \pm standard deviation (n=10) or percentages.

Abbreviations: ADHD, attention deficit/hyperactivity disorder; WISC-III/IV, Wechsler Intelligence Scale for Children III/IV; SD, standard deviation; IQ, intelligence quotient.

a combination of methylphenidate and atomoxetine (18 and 60 mg/day, respectively, $n=1$), a combination of atomoxetine and aripiprazole (35 and 9 mg/day, respectively, $n=1$), and a combination of methylphenidate and risperidone (18 and 6 mg/day, respectively, $n=1$), while three subjects were drug-naïve. Treatment with these drugs was stable for the 4 weeks prior to enrollment, and was stable during the trial. The Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)²⁰ was conducted to exclude any current, past, personal, or familial history of mental illness. Two subjects were also diagnosed as having a learning disorder: one subject was diagnosed with tic disorders, and one with learning and tic disorders, according to the DSM-IV criteria.¹⁹

Measurement of clinical symptoms

All patients were assessed using the ADHD Rating Scale IV (ADHD-RS), Japanese version.²¹ The ADHD-RS is a reliable and easy-to-administer instrument both for diagnosing ADHD in children and adolescents and for assessing treatment response. It consists of 18 items, with the scale being linked directly to DSM-IV diagnostic criteria for ADHD.²² The Das–Naglieri Cognitive Assessment System (DN-CAS), Japanese version,²³ was used to assess cognitive function. The DN-CAS is an assessment battery designed to evaluate cognitive processing. It was developed to integrate theoretical and applied psychological knowledge, using cognitive processing theory and tests, designed to measure planning, attention, and simultaneous and successive processing (PASS) in individuals aged 5–17 years. The Wechsler Intelligence Scale for Children third/fourth editions (WISC-III/IV),^{24,25} Japanese versions, were used to assess the full intelligent quotient of all patients.

Statistical analysis

Statistical analyses were performed using the software package SPSS version 21.0 for Macintosh (IBM Armonk, NY, USA). The data show means \pm standard deviation. Student's paired *t*-test was used to compare changes from baseline to 4 weeks. The Wilcoxon signed-rank test was used as a post hoc test to compare changes from baseline to 4 weeks. Values of $P<0.05$ were considered statistically significant.

Results

The baseline scores and mean changes of primary and secondary outcomes from the 4-week trial of tipepidine in ADHD subjects are shown in Table 2. A comparison of baseline scores and 4-week end-point scores showed

Table 2 Baseline scores and mean changes of primary and secondary outcomes after a 4-week trial of tipepidine in ADHD subjects

	Baseline mean \pm SD	Week 4 mean \pm SD	P-value (df, t-score)
ADHD-RS total score	30.2 \pm 9.9	16.4 \pm 8.4	<0.001* (9, 11.8)
ADHD-RS hyperimpulsive subscore	11.2 \pm 7.1	5.0 \pm 4.1	<0.001* (9, 5.7)
ADHD-RS inattentive subscore	19.0 \pm 3.6	10.6 \pm 3.8	<0.001* (9, 10.6)
DN-CAS total score	81.1 \pm 20.0	87.6 \pm 21.6	0.093 (9, -1.88)
DN-CAS planning subscore	89.2 \pm 16.6	94.0 \pm 16.4	0.164 (9, -1.52)
DN-CAS attention subscore	81.3 \pm 22.4	89.5 \pm 23.1	0.262 (9, -1.20)
DN-CAS simultaneous subscore	83.8 \pm 18.3	91.8 \pm 25.0	0.137 (9, -1.63)
DN-CAS successive subscore	89.8 \pm 20.0	89.9 \pm 14.4	0.981 (9, -0.03)

Notes: * $P<0.05$. Student's paired *t*-test was used to compare changes from baseline to 4 weeks. Wilcoxon signed-rank test was used as a post hoc test to compare changes from baseline to 4 weeks.

Abbreviations: ADHD, attention deficit/hyperactivity disorder; SD, standard deviation; df, degrees of freedom; ADHD-RS, Attention Deficit/Hyperactivity Disorder-Rating Scale IV (Japanese version); DN-CAS, Das–Naglieri Cognitive Assessment System (Japanese version).

that all the ADHD-RS scores (total scores, hyperimpulsive subscores, and inattentive subscores) improved significantly ($P<0.001$). The Wilcoxon signed-rank test also detected statistical significance in all ADHD-RS scores ($P<0.005$). However, a comparison of baseline scores and 4-week end-point scores found that none of the DN-CAS scores (total scores and planning, attention, simultaneous, and successive subscores) showed significant change. The Wilcoxon signed-rank test also failed to detect statistical significance in any DN-CAS score changes.

Tipepidine was well tolerated, with no patients discontinuing medication because of side effects. No significant effects were revealed in blood parameters, urine analysis, weight, height, blood pressure, or cardiac frequency during the 4-week follow-up period.

Discussion

Tipepidine improved the ADHD symptoms of inattention and hyperimpulsivity, as shown by ADHD-RS scores. To our knowledge, this is the first report demonstrating the beneficial effect of tipepidine in treating pediatric ADHD subjects.

Comparisons of all baseline DN-CAS scores (total scores and planning, attention, simultaneous, and successive subscores) and 4-week end-point scores detected no

significant differences. However, a comparison of baseline DN-CAS total scores and 4-week end-point scores did show a mild trend of improvement ($P=0.093$).

The lower improvement in DN-CAS symptomatology may have been partly due to the relatively low dosage of tipepidine used in this study (1.288 ± 0.349 mg/kg/day, Table 1), compared with that of the Fujieda et al trial in mice (20 mg/kg).¹⁷ Higher dosages may be more beneficial for ADHD symptoms, as they are associated with higher monoaminergic neurotransmission through GIRK channels. At present, the optimal dosage of tipepidine for ADHD is unknown, and defining this dosage should be the primary focus in the treatment of these patients.

The inhibition of GIRK channels by tipepidine is predicted to modulate brain monoamine levels in a similar manner to psychostimulants and selective norepinephrine-reuptake inhibitors. However, this trial found none of the side effects typically associated with psychostimulants and selective norepinephrine-reuptake inhibitors. Tipepidine has been used safely as an over-the-counter antitussive for children and adults in Japan since 1959. Therefore, safety issues will be no of no concern if this is used as a new treatment for ADHD.

Very recently, Hamasaki et al showed that tipepidine activated dopamine neurons in the ventral tegmental area through the inhibition of GIRK channel-activated currents, and their preliminary microdialysis study showed that tipepidine dramatically increased dopamine levels in the shell of the nucleus accumbens (NAc).²⁶ In addition, Costa Dias et al identified the possible involvement of NAc connections in the pathophysiology of impulsive decision making in ADHD, using functional connectivity magnetic resonance imaging.²⁷ Therefore, further detailed studies of tipepidine use in ADHD are needed to investigate dopamine activation in the NAc and its neural pathways.

The main limitation of this study was the small sample size ($n=10$). The second limitation was the low proportion of drug-naïve subjects. Further studies with greater analytical power, larger sample sizes, and more drug-naïve subjects will be necessary.

Conclusion

In conclusion, our pilot study suggests that tipepidine therapy may prove to be an effective alternative treatment for pediatric patients with ADHD, and since this drug is already in wide clinical use for other conditions, there should be no ensuing safety issues. However, the safety of long-term tipepidine use needs to be evaluated carefully, since many antitussive

medications are completed within 1 week. Nonetheless, more detailed randomized, double-blind studies are needed to confirm tipepidine's efficacy and safety.

Author contributions

T Sasaki and K Hashimoto drafted the manuscript. K Hashimoto is the principal investigator of this study. All authors recruited the patients, revised the article, conducted the statistical analysis, approved the final manuscript, and agreed to be accountable for all aspects of the work.

Acknowledgments

The authors are very grateful to Aya Tano and Nao Miyazaki (Chiba University), for their valuable advice on the use of DN-CAS. The authors thank Kaoru Ikeda, Chisako Fujishiro, Kimika Akiba, Natsuko Tateshouji, Komako Ito (Chiba University), the staff of the Department of Pharmacy, Chiba University Hospital, and Chiba University Hospital Clinical Research Center for their assistance with this trial.

Disclosure

The authors report no conflicts of interest in this work.

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