


The lowest effective plasma concentration of atomoxetine in pediatric patients with attention deficit/hyperactivity disorder

A non-randomized prospective interventional study

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Abstract

Background: Atomoxetine (ATX) is used as a first-line, non-stimulant treatment for attention-deficit/hyperactivity disorder (ADHD), although no studies have systematically examined the relationship between plasma concentration and clinical efficacy. We conducted this non-randomized prospective interventional study to examine the relationship between plasma concentration of ATX and clinical efficacy.

Methods: Forty-three ADHD pediatric patients received ATX, and the steady-state through plasma concentration of the last daily dose that was maintained for at least 4 weeks were determined by high-performance liquid chromatography.

Results: The receiver operating characteristic curve suggested that when plasma concentration exceeded 64.60 ng/mL, scores on the ADHD-Rating Scale improved by 50% or more ($P = .14$). Although 6 of the 8 final responders were unresponsive at the initial dose ($.72 \pm .04$ mg/kg [mean \pm standard deviation]), they responded after increasing the ATX dose to the final dose ($1.52 \pm .31$ mg/kg). Excluding 7 outlier participants, the concentration was 83.3 ± 32.3 ng/mL in 7 responders and was significantly higher than 29.5 ± 23.9 ng/mL ($P < .01$) for the 29 non-responders.

Conclusions: These results suggest that a minimum effective plasma concentration of ATX is required to achieve sufficient clinical efficacy. We hypothesized a mechanism that results in the realization of a clinical effect when the plasma concentration exceeds a certain threshold in the potential response group, whereas will not improve even if the plasma concentration is increased in the unqualified non-responder group.

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This study was approved by the Niigata University Genetic Ethics Review Committee (H23-516, G2019-0039), and registered in UMIN-CTR (<https://www.umin.ac.jp/ctr/index-j.htm>) with trial ID UMIN000035417. The full trial protocol is available via Niigata University Genetic Ethics Review Committee.

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Abbreviations: ATX = atomoxetine, ADHD = attention deficit/hyperactivity disorder, ADHD-RS = ADHD Rating Scale, HPLC = high-performance liquid chromatography, MPH = methylphenidate, ROC curve = receiver operating characteristic curve.

Keywords: ADHD, atomoxetine, lowest effective concentration, plasma concentration, ROC curve

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neuro-developmental disorder that affects 5% of children and adolescents and 2.5% of adults worldwide.^[1] Its essential feature is a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development.^[2] Throughout an individual's lifetime, ADHD can increase the risk of other psychiatric disorders, educational and occupational failure, accidents, criminality, social disability, and addictions.^[1] Although the national guidelines^[3–6] specify stimulants as first-line drugs, under some circumstances stimulants are difficult to use due to their unique disposition. Atomoxetine (ATX) is a representative non-stimulant and is positioned as a first-line drug in situations where stimulants cannot be used. Since the discontinuation of ATX for perceived lack of efficacy ranged from 8.4% to 26%,^[7] it is important to present the minimum effective blood concentration or the minimum effective dose to prevent interruption before administration with a sufficient dose and a sufficient period. Although many studies^[8,9] have examined the relationship between plasma concentration and the clinical effects of selective serotonin reuptake inhibitors, few studies have examined the relationship between plasma levels and clinical effects for ATX. ATX is a selective noradrenaline reuptake inhibitor that was originally developed as an antidepressant,^[10] and is known to be metabolized by cytochrome P450 2D6. Similar to selective serotonin reuptake inhibitors, the existence of the minimum effective concentration is expected for ATX but has not yet been investigated. We conducted this non-randomized, open-labeled, prospective interventional study to clarify the relationship between the plasma concentration and clinical efficacy of ATX.

2. Methods

2.1. Participants and research design

The participants of this study were child patients with ADHD, who were treated at the Department of Psychiatry, Niigata University Medical and Dental Hospital, Niigata, Japan. The inclusion criteria were being diagnosed with ADHD according to Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5)^[2] criteria, being 6 to 17 years old, given written informed consent by their parents/guardians, and also given written informed assent by himself/herself. The exclusion criteria were being under 6 years old, being 18 years old and over, or having comorbidities such as schizophrenia, depressive disorder, bipolar disorder, anxiety disorder, and obsessive-compulsive disorder. Comorbidities such as intellectual disability, autism spectrum disorder, specific learning disorder, tic disorder, oppositional defiant disorder, and conduct disorder were not excluded due to their high frequency. A total of 77 patients were evaluated for eligibility, and 76 patients were enrolled in the study after receiving an explanation of the aims and the procedures and providing written consent for the purpose of

publication. The sample size was determined by enrolling all patients who obtained consent during the study period. Patients who declined to participate did not receive allocated intervention, lost to follow-up, made protocol violation, or had concomitant medications were excluded from the final statistical analysis.

This study was conducted in accordance with the Declaration of Helsinki and the relevant regulations of Niigata University. This study was approved by the Niigata University Genetic Ethics Review Committee (H23-516, G2019-0039), and registered in UMIN-CTR (<https://www.umin.ac.jp/ctr/index-j.htm>) with trial ID UMIN000035417. The date of approval by the Ethics Review Committee and the start date of the study was January 24, 2012, and the final follow-up date was January 23, 2017, which was stipulated as 5 years from the approval of the Ethics Review Committee.

A non-randomized prospective intervention study, which is necessary and sufficient to determine the minimum effective plasma concentration from the receiver operating characteristic (ROC) curve, was adopted as the study design. Treatment was not blinded due to technical constraints and was open-labeled to patients, clinicians, and evaluators (parents). Participants were first administered .5 to .8 mg/kg of ATX and the dose was increased every 2 weeks up to 1.8 mg/kg, with the exceptional cases in which side effects emerged. We assessed the clinical symptoms of ADHD by every 2 weeks, using the Japanese Edition of the ADHD Rating Scale (ADHD-RS)^[11] reported by parents. The patient was defined as responsive if the total ADHD-RS score was reduced by more than 50%. For patients who responded to the treatment, the ATX dose was not increased but was instead maintained, until the blood sampling for plasma concentration measurements was completed.

2.2. Determination of plasma ATX concentrations

The primary outcome of this study is the plasma concentration of ATX, and the secondary outcomes are the relationships between ATX concentration and clinical effects. Plasma concentrations of ATX were measured using high-performance liquid chromatography (HPLC), measuring the steady-state plasma levels of the last daily dose that was maintained for at least 4 weeks. To measure the trough value, blood was sampled approximately 12 hours after the last dose, using Venoject tubes (7 mL, Terumo Japan, Tokyo, Japan) containing EDTA-Na. Samples were centrifuged at 3000 rpm (2000×g) for 10 minutes, within 3 hours of collection, and plasma aliquots were stored at –80° until assayed to determine ATX plasma concentrations.

The HPLC method used to determine the plasma concentration of ATX was developed in our laboratory.^[12] The following were added to 1000 µL of each plasma sample: 500 µL 0.5 M NaOH, 100 µL internal standard solution (trifluoperidol 10.8 µg/mL), 100 µL methanol, and 2500 µL pure water. After the extraction solvent was added, the organic phase was evaporated in vacuo, at 40°C, to dryness. The residue was dissolved in 300 µL diluting and dissolving solution, and a total of 100 µL was injected into

Table 1
Characteristics of the responder and non-responder groups.

	Non-responder (n=35)	Responder (n=8)	P value	95% Confidence interval
Age (years)	8.51±2.47	10.13±1.89	.061	-.09 to 3.31
Gender (male/female)	31/4	8/0	.315	
Body weight (kg)	31.1±9.7	36.9±10.9	.199	-3.6 to 15.1
ADHD-RS at baseline	29.2±11.4	33.3±6.5	.195	-2.2 to 10.3
ADHD-RS at steady state	25.5±10.5	14.3±5.1	<.01*	-16.5 to -6.0
Treatment period (weeks)	13.0±10.9	10.9±3.8	.365	-6.7 to 2.5
ATX dose (mg/kg)	1.43±.37	1.51±.29	.521	-.18 to .34
ATX concentration (ng/mL)	140.8±334.6	129.1±132.9	.874	-162.1 to 138.5

All values are presented as the mean±SD except for gender. The chi-squared test was used for gender and the Mann–Whitney *U* test was used for all other factors.

ADHD=attention-deficit/hyperactivity disorder, ADHD-RS=ADHD Rating Scale, ATX=atomoxetine.

**P*<.05.

the HPLC system. The HPLC system consisted of an SPD-10A ultraviolet spectrophotometer (Shimadzu Corporation, Kyoto, Japan) and an STR-ODS II column (150 mm × 4.6 mm I.D., 5 μm, Shimadzu Corporation). The mobile phase consisted of phosphate buffer (.02 M, pH=4.6), acetonitrile, and perchloric acid (60%) (61.0:38.5:5, v/v/v). The lower limit of detection was 2.5 ng/mL, and the values of the intra- and inter-assay coefficients of variation were less than 10%, at all calibration curve concentrations (21.9–1400 ng/mL) for ATX.

The major metabolites of ATX are 4-hydroxyatomoxetine and N-desmethyloxyatomoxetine, however, only 4-hydroxyatomoxetine is the active metabolite. When ATX was administered to pediatric individuals, the plasma concentration was 26 times higher than that of 4-hydroxyatomoxetine, and the effect of 4-hydroxyatomoxetine on the clinical effect was limited.^[13,14] Therefore, the plasma concentration of 4-hydroxyatomoxetine was not measured in this study.

2.3. Data analyses and statistics

Independent samples *t* test was used to test the difference. The ROC curve and the chi-squared test were used to evaluate the relationship between the plasma levels and the reduction of clinical symptoms. The sample was assumed not to meet homoscedasticity for the *t* test, and the confidence level for the ROC analysis was 95%. A *P* value of less than .05 was regarded to be statistically significant. All analyses were performed using IBM SPSS Statistics 24 (IBM Japan, Tokyo, Japan).

3. Results

Of the 76 enrolled patients, 5 did not receive the allocated treatment (4 hoped other medications, 1 patient refused to take ATX), and 71 received ATX administration. Of these, 22 participants discontinued visits, the remaining 49 completed treatment and underwent ATX plasma concentration measurements. No case of discontinuation due to adverse events was recorded. There were 3 protocol violators who could not be analyzed, such as not taking ATX the day before sampling or not submitting ADHD-RS, and these 3 cases were excluded from the analyses. During the study period, 1 participant had to use paroxetine, which strongly inhibits CYP2D6, and 2 participants also used methylphenidate, which was confused with the effect of ATX and could not be evaluated properly. These 3 cases were also excluded from the analyses. Other than these 3 individuals,

none were using concomitant medications that would affect ATX metabolism and/or symptom evaluation. A total of 43 cases were included in the statistical analyses.

The characteristics of the responder and non-responder groups and detailed results of *t* test are shown in Table 1, and the ROC curve created from the cumulative response rate and the cumulative non-response rate is shown in Figure 1. The Youden index had the highest value at the point of $x=.771$, $y=.125$ on the ROC curve, and a cutoff value of 64.60 ng/mL ($P=.014$) was estimated. When the chi-squared test was performed, combined with a cross-tabulation, significantly more ATX-responsive cases were observed among patients with plasma concentrations above 64.60 ng/mL ($P<.01$). Although 6 of the 8 final responders were unresponsive at the initial dose ($.72±.04$ mg/kg, mean ± standard deviation), they responded after increasing the ATX dose to the final dose ($1.52±.31$ mg/kg). Twenty-one of the 23 final non-responders showed plasma concentrations less than 64.60 ng/mL, even when the final dose was administered. When Tukey box plot was generated, 7 outliers were identified with scores 1.5-fold greater than the H-spread from the upper hinge, and 6 of these 7 outliers were non-responder. The ATX concentrations in the responder and non-responder groups were $129.1±132.9$ ng/mL and $140.8±334.6$ ng/mL, which were not significantly different (Table 1). However, excluding these 7 outlier participants, the concentration was $83.3±32.3$ ng/mL in responders, and was significantly higher than $29.5±23.9$ ng/mL ($P<.01$) for the non-responders (Table 2). The final dose of 7 responders excluding outliers was $1.55±.28$ mg/kg.

Of the 43 participants included in the final analysis, 16 cases (37.2%) of tachycardia, 9 cases (20.9%) of insomnia, 8 cases (18.6%) of nausea, 7 cases (16.3%) of decreased appetite, 4 cases (9.3%) of headache, 2 cases (4.7%) each of abdominal pain and somnolence, and 1 case (2.3%) each of vomiting, constipation, aggression, mood discomfort, and palpitation were reported. Weight loss, diarrhea, dizziness, tics, tremor, depression, and increased blood pressure were not reported by any patient. ROC curves were also created between the occurrence of each adverse event and ATX plasma levels, although none of the ROC curves could estimate the cutoff value associated with the adverse event.

4. Discussion

The results of this study showed that pediatric patients were more likely to respond to ATX treatment when the steady-state through plasma ATX concentration exceeded 64.60 ng/mL. Since

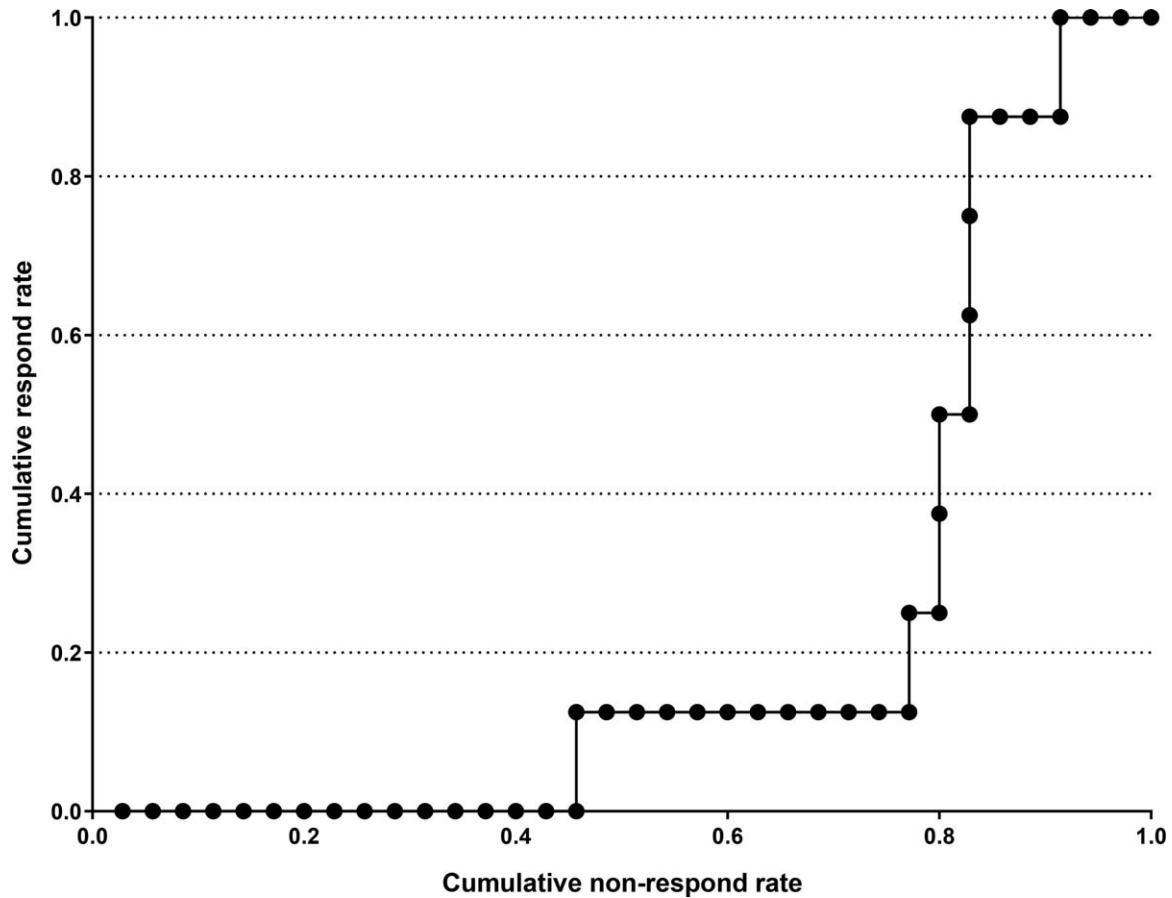


Figure 1. ROC curve of respond and concentration of atomoxetine. The right side of the x-axis shows a higher plasma concentration. The lowest effective plasma atomoxetine concentration of 64.60 ng/mL ($P = .014$) was estimated based on the ROC curve at the point of $x = .771$ and $y = .125$. ROC curve = receiver operating characteristic curve.

there were no serious adverse events or interruptions due to adverse events within the plasma concentration range observed during the study, increasing the ATX dose beyond this minimum effective plasma concentration is reasonable also in general clinical practice. Conversely, at plasma concentrations below this, ATX is more likely to fail to fully exert its potential effect. Considering external applicability, the plasma concentration of ATX cannot be measured easily in many clinical settings; however, the responder-associated dose (excluding outliers) of

$1.55 \pm .28$ mg/kg identified in this study may be helpful to clinicians. This responder-associated dose may be 1 of the targets when titrating ATX in general clinical practice. The minimal adverse events in this study mean that ATX can be escalated to the above target dose relatively safely, even in clinical situations where ATX plasma levels cannot be measured.

Several case reports describing individuals with poor or intermediate CYP2D6 metabolic ability have indicated higher plasma concentrations of ATX, and among these patients, the

Table 2

Characteristics of the responder and non-responder groups (excluding outliers).

	Non-responder (n = 29)	Responder (n = 7)	P value	95% Confidence interval
Age (years)	8.41 ± 2.43	9.57 ± 1.13	.077	-.14 to 2.45
Gender (male/female)	25/4	7/0	.297	
Body weight (kg)	30.4 ± 9.6	34.3 ± 8.8	.327	-4.5 to 12.3
ADHD-RS at baseline	29.8 ± 10.9	33.4 ± 6.9	.291	-3.5 to 10.7
ADHD-RS at steady state	27.0 ± 10.7	14.0 ± 5.5	<.01*	-19.0 to -7.0
Treatment period (weeks)	13.6 ± 11.9	11.3 ± 3.9	.385	-7.7 to 3.1
ATX Dose (mg/kg)	$1.44 \pm .37$	$1.55 \pm .28$.414	-.17 to .38
ATX Concentration (ng/mL)	29.5 ± 23.9	83.3 ± 32.3	<.01*	23.6 to 84.0

All values are presented as the mean \pm SD except for gender. The chi-squared test was used for gender and the Mann-Whitney U test was used for all other factors.

ADHD = attention-deficit/hyperactivity disorder, ADHD-RS = ADHD Rating Scale, ATX = atomoxetine.

* $P < .05$.

efficacy of ATX was also increased, as well as the incidence of adverse events do.^[15–17] To the best of our knowledge, only Hazell et al^[18] investigated systematically the relationship between the ATX concentration and clinical effects. However, they defined the response case using oppositional defiance disorder subscale of the Swanson, Nolan, and Pelham Teacher and Parent Rating Scale, and the Clinical Global Impression-Improvement scale, and they did not evaluate the clinical symptoms of ADHD; thus, this study is the first one to systematically examine the relationship between ATX plasma levels and the clinical symptoms of ADHD. Although Hazell et al^[18] concluded that plasma concentrations did not predict ADHD symptom improvement, they only compared the mean ATX plasma concentrations of the responder and the non-responder groups, without investigating the ROC curve. In contrast with our study, Hazell et al^[18] only collected blood samples 60 to 90 minutes after ATX administration, to examine the peak plasma concentration. These methodological differences may explain the differences between our results and the results of their study.

The results of the present study were similar to the results reported for fluvoxamine by Suzuki et al^[9] suggesting that ATX concentrations must reach a minimum effective level to exert sufficient clinical effects. Assuming a sigmoid non-linear model for the relationship between plasma concentrations and clinical effects identically to the dose-response curve, 64.60 ng/mL is the assumed minimum effective plasma concentration for ATX. Many researchers consider ADHD to be a pathologically heterogeneous syndrome,^[1,19] and different groups with different pathologies are naturally expected to respond differently to ATX. This sigmoid non-linear model indicates that factors other than plasma concentration are likely to define the potential responder group and unqualified non-responder group to ATX. There is a mechanism proposed; in which the clinical effect appears when the ATX concentration exceeds the minimum effective concentration in the potential responder group, whereas the unqualified non-responder group is unlikely to improve regardless of plasma ATX concentration. The fact that 6 of the 7 participants with outliers in ATX plasma levels were non-responders is also consistent with this expected mechanism.

The limitations of this study include small sample size, being a single institutional study, lack of genetic analysis, and low response rates. Larger sample size studies should be conducted to confirm the reproducibility of the main results. During the analysis of adverse events, no association was found between adverse event occurrence and plasma ATX concentrations. However, increasing the sample size may result in different results. Since a single institution study can be a potential bias, the main results need to confirm the reproducibility through the studies with larger sample sizes or multicenter studies. Although CYP2D6 is known to play a major role in the metabolism of ATX, gene analysis, including CYP2D6, was not performed in this study. The high frequency of individuals carrying CYP2D6*10 among Japanese has been reported,^[20,21] and it can be a potential bias that all the subjects in this study were Japanese. Further studies with a larger sample size and multiracial population should be conducted to confirm the reproducibility of the main results. In the future, examining ADHD individuals whether the potential responder or unqualified non-responder by the relationship among gene polymorphisms, ATX plasma concentrations, and clinical effects would be interesting. While many studies defined a 30% improvement in

ADHD-RS score as a response, this study defined a 50% improvement as a response to eliminate the effects of the placebo effect. The lower response rate in this study than in other studies is due to this definition of response, however, it was considered necessary to eliminate the placebo effect and obtain more accurate results. On the other hand, examining the results at low response rates cannot rule out the possibility of unintended bias in the results. Therefore, the interpretation of the results should be done carefully.

5. Conclusion

ATX may require a minimum effective plasma concentration to exert clinical effects. When treating ADHD individuals with ATX, measuring ATX concentrations may be useful to design personalized treatment plans that are suitable for individual patients. Future research examining the relationship between ATX plasma concentrations and treatment efficacy may elucidate components of the pathological mechanisms underlying ADHD, which is considered to be a heterogeneous syndrome.

Author contributions

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