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Dose-response analysis of aripiprazole in patients with schizophrenia in Taiwan

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Abstract

Background: Aripiprazole is a third-generation antipsychotic agent with acceptable efficacy and a good safety profile. Previous studies have indicated the therapeutic serum concentration of aripiprazole to be 100 to 350 ng/ml; however, most of these studies examined a Western population. Patients with schizophrenia from Tungs' Taichung MetroHarbor Hospital in central Taiwan were recruited to analyze the dose–response relationship of aripiprazole in the Chinese population.

Objective: We aimed to investigate whether a serum concentration of aripiprazole higher than the current suggested range leads to higher response rates.

Design: A prospective cohort study was designed to investigate the response rates in different studied cohorts grouped by serum concentration of aripiprazole.

Data Sources and Methods: Data of 64 patients who presented to a single medical center in central Taiwan and who received therapeutic drug monitoring (TDM) were obtained. Serum concentrations of aripiprazole were correlated with the clinical response of patients by using the Clinical Global Impressions (CGI) scores.

Results: The mean concentration of aripiprazole was 432.1 ± 275.1 ng/ml in the study cohort. Among the much-improved patients, the mean serum concentration of aripiprazole was 494 ± 273 ng/ml (25th–75th percentiles 264–666 ng/ml), which was higher than the current recommended therapeutic target of 100–350 ng/ml for aripiprazole. The response rate in the severe group (baseline CGI score of 6 or 7) was significantly higher than in the moderate group (baseline CGI score of 4 or 5; 86.7% *versus* 55.9%, $p = 0.007$).

Conclusion: A significantly higher response rate was observed in the study cohort with serum aripiprazole concentrations over 300 ng/ml. Therefore, dosing higher than the current recommended range may potentially improve the treatment efficacy in the Chinese population. Because the serum concentration varies among patients due to multiple intrinsic and extrinsic factors, TDM, especially in outpatients, is recommended if the clinical response is limited.

Keywords: antipsychotic drug, aripiprazole, therapeutic dose monitoring, trough serum concentrations

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Background

Aripiprazole is a third-generation antipsychotic drug commonly prescribed for treating schizophrenia. The drug has a unique mechanism of action involving dopamine and serotonin receptors.[1] A previous study compared the side effects, including weight gain, extrapyramidal side effects, prolactin increase, QTc prolongation, and sedation, of multiple antipsychotic drugs and reported that aripiprazole ranked in the top one-third of all antipsychotic drugs.[2] Because of its lower incidence of side effects, aripiprazole is frequently chosen as the first-line treatment for a first episode of psychosis, and it has exhibited acceptable efficacy.[3,4] Furthermore, aripiprazole augmentation was significantly more effective than monotherapy in a study.[5] However, the mean time to all-cause discontinuation for aripiprazole was

shorter than that of other second-generation oral antipsychotic drugs (SGAs).[6] To optimize the efficacy and further decrease the long-term discontinuation, it is crucial to perform dose–response analysis of antipsychotic drugs. With an individualized prescribing strategy coordinated with dose–response analysis and potentially related factors, acceptable efficacy with a lower discontinuation rate may be achieved.

Previous studies have determined the therapeutic serum concentration of aripiprazole and reported a heterogeneous range of 100 to 350 ng/ml.[7,8] In another study, the minimal effective daily dose of aripiprazole was 10 mg/day, with statistically significant improvements compared with placebo.[9] A recent dose–response meta-analysis of aripiprazole exhibited a slightly bell-shaped curve, indicating that the effectiveness was not always associated with higher doses.[10] To the best of our knowledge, a research gap exists in terms of the factors with predictive value that can assist clinical psychiatrists to determine the individual target dose of aripiprazole for each patient. Most studies have enrolled populations other than Han Chinese. This study enrolled patients with schizophrenia from a single medical center in central Taiwan. The objective of this study was to analyze the dose–response relationship of aripiprazole in the Chinese population.

Methods

Participants

Sixty-four patients diagnosed with schizophrenia, based on the guidelines of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, from the outpatient department or acute psychiatric inpatient ward of Tungs' Taichung MetroHarbor Hospital, a medical center in central Taiwan, between 1 January 2017 and 1 June 2018, were included in this study. Participants taking oral aripiprazole as a monotherapy or an add-on antipsychotic and those who consented to antipsychotic serum level testing were included. Participants with any prescription modification of antipsychotic agents other than aripiprazole during the study period were excluded to avoid ambiguous results.

Study treatment

Demographic data, including age, gender, diagnosis, current antipsychotic, antipsychotic dose, and length of treatment, were obtained from the clinical records. Doses and types of other psychotropic agents remained consistent during the data collection period of this study. Serum prolactin levels were assessed if the patient-reported menstruation dysregulation or sexual dysfunction. Aripiprazole dosing was initiated at 2.5 mg/day. After a 2-week adverse event–free period, the patient was included in this study, and the treating psychiatrist could increase the dose of aripiprazole. Dose titration was performed in the following 4 weeks, and the final dose of aripiprazole depended on the clinical judgment of the treating psychiatrist.

Sample collection and analysis

Blood samples were collected after the daily dose of aripiprazole remained consistent for more than 28 days. Blood samples (5 ml) were extracted from the cubital vein of consenting participants between 9 am and 10 am (12–13 hours after the last medication dose). The serum concentrations of aripiprazole were determined through high-performance liquid chromatography (HPLC) and HPLC-tandem mass spectrometry methods (isRed Pharma & Biotech Research Co., Ltd., Taichung, Taiwan), and the therapeutic drug monitoring (TDM) method was validated by the Taiwan Food and Drug Administration.

Study assessment

Participants were evaluated on the day of inclusion and the day of blood sample collection, which was the 28th day after dose modification was accomplished. The effectiveness of the drug was evaluated using the Clinical Global Impression Scale Severity of Illness (CGI-S) score. Additional effectiveness measures included the CGI response rate, which is defined as a CGI score of no more than 2 at the second assessment time point or an improvement of CGI score of more than 2 compared with the score at the first assessment time point. All rating scales were completed by the treating psychiatrists.

Statistical analysis

All statistical analyses were performed using SPSS 25 (version 25, SPSS Inc., Chicago, USA). Descriptive statistics for continuous variables were presented as mean ± standard deviation, and categorical variables were represented as numbers (n) and percentages (%). An independent t-test was

Table 1. Demographic and clinical characteristics of study participants.

Serum concentration	Low, ⩽300 ng/ml	High, >300 ng/ml	t/χ^2	*p*
N (%)	26 (40.6)	38 (59.4)		
Responder, *n* (%)	13 (50)	32 (84.2)	8.655	**0.003**
Male gender, *n* (%)	10 (38.5)	10 (26.3)	1.060	0.411
Acutely ill, *n* (%)	0 (0)	8 (21.1)	6.256	**0.012**
Age, mean (SD)	35.2 (14.9)	34.3 (11.3)	0.295	0.769
Body weight (kg), mean (SD)	67.2 (12.0)	64.2 (13.2)	0.929	0.357
Dose (mg/d), mean (SD)	15.5 (7.6)	25.7 (7.6)	−5.237	<**0.001**
Baseline CGI-S score, mean (SD)	5.1 (0.7)	5.6 (0.7)		**0.009**
Post-treatment CGI-S score, mean (SD)	3.6 (1.0)	3.1 (0.9)		0.055

CGI-S, Clinical Global Impression Scale Severity of Illness; SD, standard deviation.
Bold p-values indicate a statistically significant difference.

used to examine the relationship between the variables affecting the treatment response. Categorical data were compared using the chi-square test or Mann–Whitney *U* test, and continuous data were compared using Student's *t*-test. Pearson correlation analysis was used to examine the correlation between the continuous variables. Logistic regression was used to analyze the influence of variants on symptom severity. The significance level for all statistical analyses was $p < 0.05$.

Results

According to the *International Classification of Diseases, Tenth Revision* (World Health Organization), all 64 participants suffered from schizophrenia disorder (F20).

In this study, 59.4% of the participants had a serum aripiprazole concentration higher than 300 ng/ml, and the number of responders was significantly higher in the high serum aripiprazole concentration group ($p = 0.003$). Details of demographic and clinical characteristics are provided in Table 1. Among the patients with serum aripiprazole concentrations higher than 300 ng/ml, 26.3% were males and 21.1% were acutely ill and hospitalized; the mean age was 34.3 (SD = 11.3) years, and the mean body weight was 64.2 kg (SD = 13.2). The proportion of acutely ill and hospitalized patients was significantly higher in the high serum aripiprazole concentration group ($p = 0.012$); however, the mean age and body weight exhibited no significant differences between the two groups. The mean daily dose of aripiprazole ($p < 0.001$) and baseline CGI-S score ($p = 0.009$) were significantly higher in the high serum aripiprazole concentration group, but no significant difference was observed in the post-treatment CGI-S score between the two groups.

Complete information on treatment efficacy was available for each patient. After a 4-week steady-state administration of aripiprazole therapy, serum levels were measured for 64 patients from a single hospital between 1 May 2017 and 31 May 2018. The patients were markedly ill at the baseline measurement [CGI-S (mean ± SD) 5.39 ± 0.76] with variable responses to aripiprazole treatment (CGI-I 2.13 ± 1.18).

The oral daily dose of aripiprazole ranged between 7.5 mg/day and 30 mg/day, and the mean daily dose was 21.5 ± 9.0 mg/day. The mean aripiprazole serum concentration of 432.1 ± 275.1 ng/ml (range 74.9–1371.8 ng/ml; 25th–75th percentiles 213.8–651.3 ng/ml) was obtained. The mean dose-corrected aripiprazole concentration (concentration-to-dose ratio) was 20.4 ± 9.4 ng/ml/mg. The dose-dependent serum concentrations are plotted as box plots in Figure 1. The correlation coefficient between the prescribed daily dose and resulting serum concentrations in the inpatient group and outpatient group were 0.781 ($p = 0.013$) and 0.567 ($p < 0.001$), respectively.

The patients were divided into an inpatient group ($N = 9$) and an outpatient group ($N = 55$); the

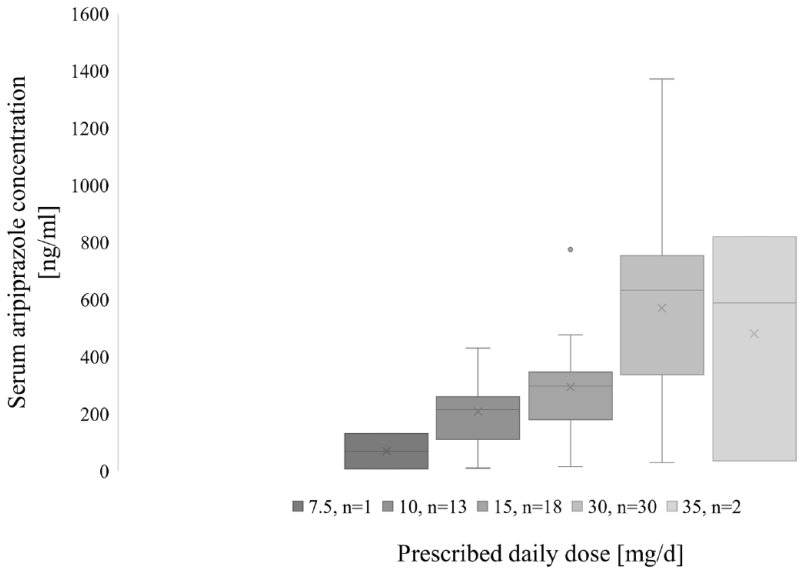

Figure 1. Box plot of the correlation of aripiprazole serum concentrations with the given dose.

mean aripiprazole serum concentration of these two groups was 695.4 ± 159.5 ng/ml and 389.0 ± 266.0 ng/ml, respectively. The mean dose-corrected aripiprazole concentration was higher, but not significantly so, in the inpatient group (26.20 ± 4.39 ng/ml/mg) than in the outpatient group (19.58 ± 9.88 ng/ml/mg; $t = 1.858$, $p = 0.068$).

Overall, the aripiprazole therapy in the study cohort was significantly effective ($t = 14.303$, $p < 0.001$). The average baseline CGI-S and post-treatment CGI-S of all participants were 5.39 (SD = 0.769) and 3.27 (SD = 0.963), respectively. The patients were divided into mild, moderate, and severe groups based on baseline CGI-S scores of less than 4 (0%), 4 to 5 (53.1%), and more than 6 (46.9%), and subgroup analysis was performed. The response rates of the moderate and severe groups were 55.9% and 86.7%, respectively. The efficacy of aripiprazole was significantly higher in the severe group ($\chi^2 = 7.236$, $p = 0.007$; Table 2).

Higher daily dose ($t = -2.846$, $p = 0.006$), dose-to-weight ratio ($t = -3.085$, $p = 0.003$), and serum concentration ($t = -2.905$, $p = 0.005$) were observed in responders than in nonresponders, as indicated by the independent t-test analysis. Other variables, including inpatient treatment, age, gender, and body weight, did not exhibit any correlation with the response rate.

Among the 64 participants whose average CGI score of improvement was 2.125 (SD = 1.18), 45 were very much or much improved (Figure 2). The mean serum aripiprazole concentration of these patients was 494 ± 273 ng/ml (25th–75th percentiles 264–666 ng/ml). Among participants with minimal or no improvement ($n = 19$), the mean serum aripiprazole concentration was 286 ± 219 ng/ml (25th–75th percentiles 132–341 ng/ml). The serum concentration of aripiprazole was significantly higher in patients with very much or much improvement ($p = 0.003$).

Discussion

In this study, the serum aripiprazole concentrations in inpatients and outpatients diagnosed with schizophrenia and treated with aripiprazole were analyzed, and the interaction of concentration with patient variables was studied. *CYP2D6* polymorphism and various phenotypes of metabolizers influence the serum concentration of aripiprazole,[11] and similar rates of elimination have been reported in Han Chinese and white participants.[12] The time required to achieve steady-state serum drug concentrations is approximately 14 days.[13] In this study, the serum drug concentrations after stable dosing for 28 days were measured to ensure a small fluctuation of serum drug concentration within a day.

Table 2. Comparison of response rate between different baseline symptom severity groups.

		Responder		Non-responder		Total		χ^2	*p*
		N	%	*N*	%	*N*	%		
Baseline symptom severity	Moderate (CGI-S = 4, 5)	19	55.9	15	44.1	34	53.1	7.236	0.007
	Severe (CGI-S = 6, 7)	26	86.7	4	13.3	30	46.9		

CGI-S, Clinical Global Impression Scale Severity of Illness.

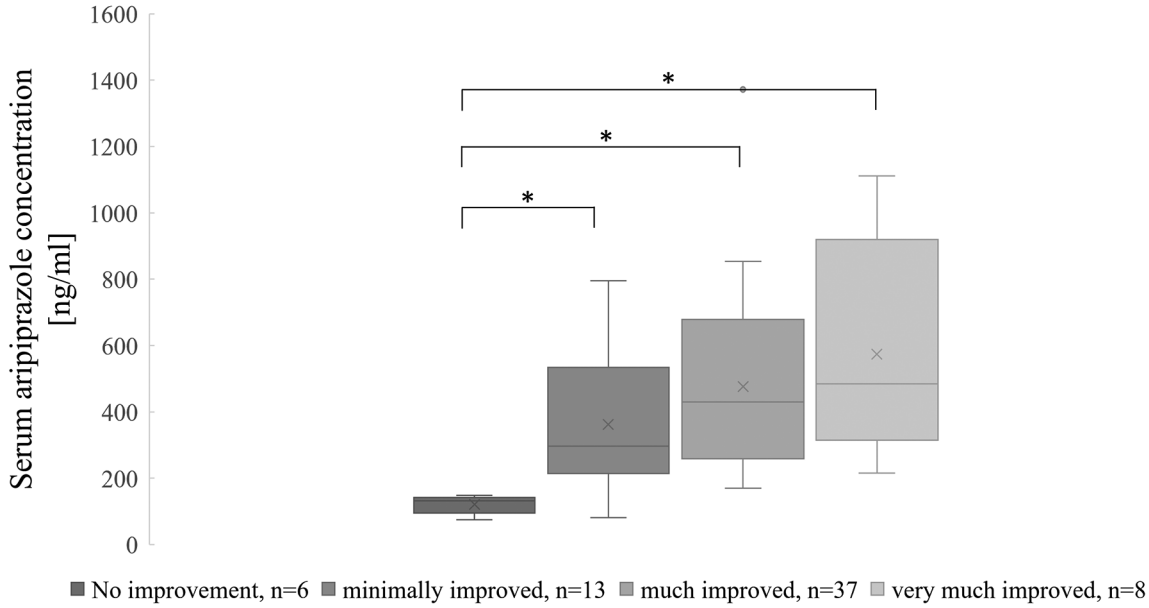

Figure 2. Box plot of the therapeutic improvement according to the Clinical Global Impression scale on improvement (CGI-I) and aripiprazole serum concentrations in 64 participants who were receiving aripiprazole as antipsychotic therapy. *$p < 0.05$.

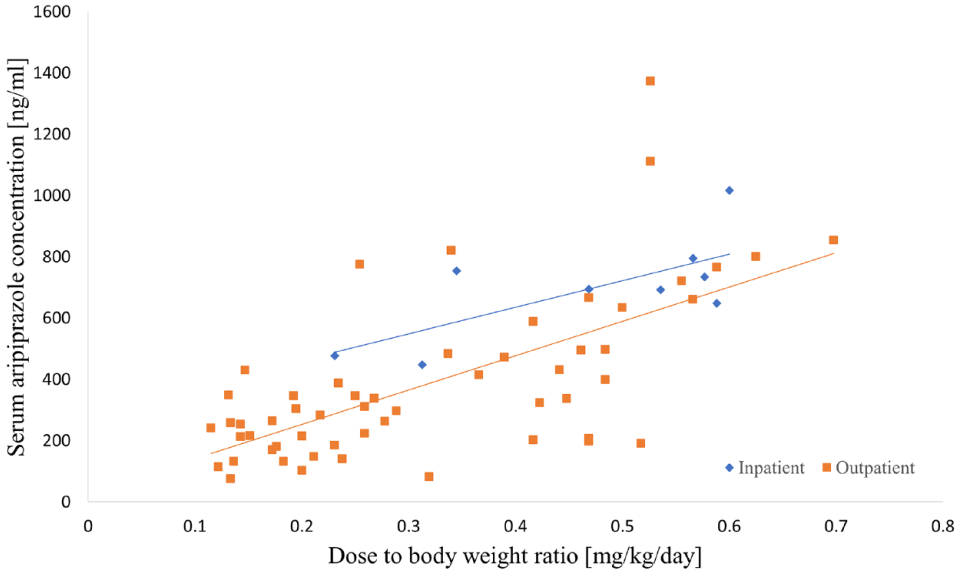

Figure 3. Dose-related serum concentrations of aripiprazole.

In patients with schizophrenia, therapeutic nonadherence due to poor disease insight, psychotic symptoms, and adverse effects leads to relatively poor prognosis and quality of life.[14,15] Adverse effects induced by antipsychotic agents, including sedation, cognitive impairment, and acute parkinsonism, have been mentioned to be associated with poor quality of life in patients with schizophrenia.[16–18] A superior profile of adverse effects was observed in the safety and tolerability analysis of aripiprazole compared with other first- and second-generation antipsychotic agents.[19] And the adverse effect of cognitive impairment was found to be not related to the prescribed dose of aripiprazole in a comparative study.[20] Based on comparable efficacy and a safer drug profile, aripiprazole has become a reliable antipsychotic medication for outpatients. In this study, a

significant correlation between prescribed dose and serum aripiprazole concentration was found in both studied groups which indicated that the drug adherence in both studied groups was acceptable. Drug adherence of inpatients and outpatients represented by dose-corrected serum concentrations were visualized in Figure 3.

However, TDM still plays an important role in clinical practice. It is recommended to perform TDM in certain circumstances – for instance, to optimize the clinical response and to reduce possible toxicity.[21,22] However, limited data speak to the cost-effectiveness of TDM, and the value of regularly assessing the serum aripiprazole concentration remains uncertain.[23] In patients with limited oral treatment adherence, a long-acting injectable form of aripiprazole may improve response to treatment.[1]

The suggested therapeutic target of serum concentration for oral aripiprazole ranged from 150 to 300 ng/ml in previous studies.[7,24] In a systemic review, a response rate of 68% was observed in patients treated within the proposed concentration range of aripiprazole.[25] Positron emission tomography (PET) studies have revealed that the striatal dopamine D2/D3 receptor were completely saturated when serum aripiprazole concentration exceeded 100–150 ng/ml.[26] A linear correlation was observed between dopamine receptor occupancy and serum aripiprazole concentration, but the serotonin receptor occupancy exhibited a negligible relationship with serum aripiprazole concentration in another study.[27] On account of its partial agonism and functional selectivity to dopamine and serotonin receptors, the efficacy of aripiprazole was attributed to a combination of pharmacological factors.[28]

Previous review articles on the dose–response relationship of aripiprazole in schizophrenia and schizoaffective disorders identified no additional benefits for doses above 20 mg/day, but the serum concentration of aripiprazole was not measured.[29] The participants of this study exhibited a much-improved level according to the CGI-I scale, and the 25th–75th percentiles of serum aripiprazole levels were 264–666 ng/ml, which are much higher than the recommended therapeutic serum aripiprazole concentration. A pharmacokinetic study in the Japanese population revealed that *CYP2D6* polymorphism may contribute to variations in drug metabolism and the clearance rate of aripiprazole.[30] Most research on the therapeutic window of aripiprazole has been performed in Western populations;[24,31] therefore, further prospective research is required to confirm the higher therapeutic window in the Chinese population.

The relationship between the therapeutic efficacy of various antipsychotic agents and the serum concentrations of patients with schizophrenia has been discussed previously. In placebo-controlled studies of aripiprazole in acute exacerbated patients with schizophrenia, significant improvements of psychotic symptoms, assessed using the Positive and Negative Syndrome Scale and CGI-S after 4–6 weeks of treatment, were observed only in groups with a daily dose of aripiprazole higher than 10 mg.[9,32,33] In a more recent study, the effectiveness of aripiprazole (20 and 30 mg/day) was compared with that of risperidone (6 mg/day) and placebo.[34] Rapid onset of efficacy in a week and no significant differences in response rates were observed between the groups of 30 mg/day aripiprazole and 6 mg/day risperidone. In this research, a significant positive correlation was observed between the serum concentration of aripiprazole and clinical improvement. Moreover, the clinical response was better in patients with higher baseline CGI scores. If clinically indicated and the patient can tolerate it, a higher daily dose of aripiprazole may potentially lead to better efficacy and greater improvement.

This study has several limitations. Although the co-medication remained consistent during the administration and modification of aripiprazole, the detailed data of several additional medications administered to each patient, including agents that may interact with *CYP3A4*, were missing. Furthermore, the profile of tolerability and side effects was not assessed in this study, although these might affect adherence to medical treatment. In addition, whether the side effects of aripiprazole are dose-dependent or not remains unclear.

In conclusion, the response rate was significantly higher in the study cohort with serum aripiprazole concentrations greater than 300 ng/ml, which is the current suggested target concentration. A prescribed daily dose higher than the current suggested dose of 10–30 mg/day is required to improve the serum concentration and treatment efficacy, especially in the Chinese population. Because the serum concentration varies among patients due to multiple intrinsic and extrinsic factors, TDM is recommended if the clinical response is limited.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Tungs' Taichung MetroHarbor Hospital (IRB no.: 105063). The authors obtained the written informed consent from the patients included in this study.

Consent for publication

Not applicable.

Author contributions

Yun Tien: Conceptualization; Data curation; Investigation; Methodology; Visualization; Writing – original draft.

Hsiang-Ping Huang: Data curation; Formal analysis; Investigation; Methodology; Software; Validation.

Ding-Lieh Liao: Formal analysis; Methodology; Validation.

Shang-Chien Huang: Conceptualization; Investigation; Methodology; Project administration; Resources; Supervision; Writing – review & editing.

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Competing Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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