CNPT The Japanese Society of Clinical Neuropsychopharmacology
Clinical Neuropsychopharmacology and Therapeutics
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Metabolic Effects of Sodium Valproate on Atypical Antipsychotics in Japanese Psychotic Patients

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ABSTRACT

Aim: To investigate the metabolic effects of atypical antipsychotics with or without sodium valproate (VPA) supplementation
Methods: The anthropometrics and metabolic markers were reviewed in 132 Japanese psychotic patients treated with olanzapine, paliperidone, or aripiprazole. The outcome values and triglyceride (TG)/high-density lipoprotein cholesterol (HDL-C) ratios reflecting insulin resistance were compared at baseline and at 3 and 6 months in VPA-non-using (-VPA) patients and VPA-using (+VPA) patients for each atypical antipsychotic.
Results: There were significant increases relative to baseline in body mass index (BMI) at 6 months in olanzapine/-VPA patients, and higher TG levels at 6 months in olanzapine/-VPA patients, olanzapine/+ VPA patients, and paliperidone/-VPA patients. The TG/HDL-C ratio at 6 months was significantly higher in olanzapine/+VPA patients and olanzapine/-VPA patients. Aripiprazole had no significant effects on these markers irrespective of whether or not VPA was used.
Conclusion: Sodium valproate may produce different metabolic effects on body weight, lipid levels, and insulin resistance when combined with various atypical antipsychotics.

Keywords: sodium valproate, atypical antipsychotics, metabolic effects, triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio

Received July 16, 2013 / Accepted October 1, 2013 / Published November 28, 2013

INTRODUCTION

Sodium valproate (VPA) is a broad-spectrum antiepileptic drug. In the psychiatry clinical setting, it is currently widely used for other indications, such as bipolar disorder, schizophrenia, and schizoaffective disorder as a mood stabilizer, combined with various types of atypical antipsychotics [1, 2]. Frequent side effects of valproate treatment include weight gain and/or metabolic effects, although their real incidence or magnitude is unknown and the exact mechanism remains unclear [3-5].
Atypical antipsychotics are also associated with metabolic disorders, and vary in their propensity to cause these adverse effects [6]. In this regard, clozapine and olanzapine have the greatest liability, followed by quetiapine, risperidone, paliperidone, aripiprazole, and ziprasidone, according to the large automated database study [7] and the Clinical Antipsychotic Trials of Intervention Effectiveness study [8]. Recent studies have suggested weight-independent effects of certain atypical antipsychotics such as olanzapine or clozapine on insulin resistance that are above and beyond obesity [9, 10].
Insulin resistance, as measured by the ratio of triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) values (TG/HDL-C), has been proposed as a superior marker of metabolic adversity compared to metabolic syndrome criteria [11,12].
Differences in the metabolic effects of VPA when

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combined with specific atypical antipsychotics have not been studied longitudinally, and the interaction between antipsychotics and VPA remains largely unexplored in Japanese psychotic subjects. We had hypothesized that the concomitant use of VPA would increase the risk of the metabolic effects compared with atypical antipsychotic monotherapy.

The aim of the present study is to investigate the risk of the metabolic effects of atypical antipsychotics with or without VPA augmentation in schizophrenia and bipolar patients, based on a 6-month retrospective review of metabolic parameters.

METHODS

Subjects

All inpatients treated with olanzapine, paliperidone, or aripiprazole with a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), Text Revision [13] were enrolled consecutively and studied retrospectively from April 2011 to September 2012 at Kusatsu Hospital in Hiroshima, Japan. Those patients who had been treated with different antipsychotics or who were antipsychotic treatment-naïve were permitted to enter this study. Throughout the 6-month observation period, the exclusion criteria included concomitant use of antipsychotics, antidepressants, mood stabilizers except VPA, and medical treatment for diseases such as diabetes mellitus and dyslipidemia, which were expected to directly affect metabolic effects. A total of 132 subjects were finally selected and divided into six groups that received atypical antipsychotic monotherapies or combination therapies.

Outcome Measures and Statistical Methods

Body weight, body mass index (BMI), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and fasting blood glucose levels were collected through routine practice at baseline and 3 and 6 months following antipsychotic treatment initiation. The ratio of TG to HDL-C values (TG/HDL-C) was assessed together with these metabolic values.

Categorical variables, including the baseline distribution of sex, psychiatric disease and reasons for dropout, were analyzed using the chi-squared test. Baseline differences of mean age, duration of illness, and the values of the metabolic markers or dropout rates between the VPA-non-using and VPA-using groups for each atypical antipsychotic were evaluated using the unpaired Mann-Whitney U test, and considered statistically significant at $P < 0.05$. Differences in the mean daily dose of each atypical antipsychotic between the VPA-non-using and VPA-using groups, and in the mean daily dose of VPA among the VPA-using groups, were also compared.

Within each subgroup, multiple comparisons of the values at baseline and 3 and 6 months were performed with repeated-measures ANOVA, followed by post-hoc analysis using Bonferroni adjustment, and considered statistically significant at $P < 0.05$.

The ethics committee of Kusatsu Hospital approved this study, and informed consent was obtained from all participants.

RESULTS

Sample Characteristics and Treatment Disposition

The baseline clinical characteristics and the dropout characteristics at 6 months of patients taking olanzapine, paliperidone, and aripiprazole with or without VPA are presented in Table 1.

Patients who received olanzapine with VPA (olanzapine/+VPA) had significantly longer durations of illness and higher daily doses of atypical antipsychotic than those who received olanzapine without VPA (olanzapine/-VPA). Although some differences were found at baseline by duration of illness and atypical antipsychotic daily dose between olanzapine without VPA and olanzapine with VPA, no differences were found at baseline in any of the parameters examined between paliperidone without VPA (paliperidone/-VPA) and paliperidone with VPA (paliperidone/+VPA), or between aripiprazole without VPA (aripiprazole/-VPA) and aripiprazole with VPA (aripiprazole/+VPA). Among VPA-using groups, there were no significant differences in the daily dose of VPA.

Of the 132 patients with baseline and follow-up data, 60.4 %, and 47.8% were retained at 3- and 6-month follow-up, respectively. Changes of atypical antipsychotic and/or VPA because of amelioration or deterioration of psychotic symptoms occurred in 13.6% of patients, and data were missing at these points because of patient discharge for 38.6% of all subjects. Dropout rates and reasons were independent of atypical antipsychotic treatment and VPA combination status.

Table 1. Baseline Clinical Characteristics and Dropout Characteristics of Patients Taking Olanzapine, Paliperidone, or Aripiprazole With or Without Sodium Valproate

Characteristic	OLZ VPA(-)	OLZ VPA(+)	OLZ intragroup comparison	PAL VPA(-)	PAL VPA(+)	PAL intragroup comparison	APZ VPA(-)	APZ VPA(+)	APZ intragroup comparison	SGA intragroup comparison
Age, y	44.1±15.3	44.4±13.1	NS	39.7±12.7	36.9±12.1	NS	49.2±17.0	46.3±19.3	NS	
Sex, n (%)			NS			NS			NS	
Male	12 (40.0)	8 (34.8)		18 (58.1)	10 (71.4)		10 (40.0)	5 (55.6)		
Female	18 (60.0)	15 (65.2)		13 (41.9)	4 (28.6)		15 (60.0)	4 (44.4)		
DSM-diagnosis, n (%)			NS			NS			NS	
Schizophrenia/ schizoaffectivedisorder	28 (93.3)	20 (87.0)		31(100.0)	14 (100.0)		18 (72.0)	4 (44.4)		
Bipolar disorder	2 (6.7)	3 (13.0)		0 (0.0)	0 (0.0)		7 (23.0)	5 (55.6)		
Duration of illness, y	12.9±9.9	18.5±10.2	†	11.5±9.3	13.6±12.3	NS	10.6±9.9	10.4±7.5	NS	
Dose, mg										
Atypical antipsychotic	14.2±5.1	17.6±5.0	†	7.7±2.7	9.0±2.9	NS	15.9±7.1	10.7±8.0	NS	
Valproate	0	800±387		0	757±352		0	767±485		NS
Dropout , n (%)	14 (46.7)	11 (47.8)	NS	15 (48.4)	9 (64.3)	NS	14 (56.0)	6 (66.6)	NS	
Dropout reason, n (%)			NS			NS			NS	
Psychotic symptom	2 (6.7)	2 (8.7)		4 (12.9)	2 (14.3)		6 (24.0)	2 (22.2)		
Ambulatory care	12 (40.0)	9 (39.1)		11 (35.5)	7 (50.0)		8 (32.0)	4 (44.4)		

Values are mean ± SD unless otherwise specified. NS = not significant, † $P = < 0.05$ for intragroup comparisons.
Abbreviations: OLZ = olanzapine, PAL = paliperidone, APZ = aripiprazole, VPA = sodium valproate

Table 2. Anthropometric and Metabolic Measures for Subjects With Follow-Up Data (N = 132) Olanzapine, Paliperidone, and Aripiprazole With or Without Sodium Valproate

Outcome Measure	Time Point, mo	OLZ VPA(-)	OLZ VPA(+)		PAL VPA(-)	PAL VPA(+)		APZ VPA(-)	APZ VPA(+)	
BW, kg	Bsaeline	49.9±2.1	59.4±3.2	†	61.1±2.0	66.0±3.0	NS	53.8±2.6	59.2±2.3	NS
	3	53.8±3.0	62.1±3.5		62.7±2.7	69.1±2.9		57.2±5.6	59.3±2.5	
	6	56.7±3.4	62.4±5.6		64.7±2.7	71.8±5.8		54.6±4.1	55.7±1.9	
BMI, kg/m^2	Bsaeline	19.5±0.6	23.3±1.1	††	22.3±0.7	22.1±0.9	NS	21.2±0.8	22.5±1.3	NS
	3	21.1±0.8	23.7±1.2		22.4±1.2	23.5±1.1		21.6±2.2	22.3±1.5	
	6	22.2±0.8 *	24.2±1.9		24.2±1.0	24.5±2.0		21.8±2.1	21.4±2.2	
TG, mg/dL	Bsaeline	77.4±7.3	84.2±6.0	NS	89.4±5.8	73.9±6.8	NS	93.6±8.0	107.4±17.6	NS
	3	98.6±12.4	99.8±13.7		108.4±13.6	91.3±10.3		95.2±7.4	103.0±21.8	
	6	120.1±18.0 *	123.7±22.6 *		124.6±15.3 *	91.0±27.4		101.4±8.5	119.7±34.9	
LDL-C, mg/dL	Bsaeline	105.7±5.2	101.0±6.2	NS	108.2±5.9	82.3±5.2	††	118.4±7.2	111.9±10.7	NS
	3	116.5±6.6	87.2±5.9		112.2±9.6	88.5±13.0		124.8±7.4	90.3±7.9	
	6	111.4±7.6	102.6±8.3		121.6±8.7	95.8±18.8		93.5±7.3	100.3±30.9	
HDL-C, mg/dL	Bsaeline	59.9±2.2	65.3±3.9	NS	59.2±2.8	52.8±3.2	NS	61.3±2.9	59.9±4.2	NS
	3	61.6±4.9	54.5±4.2		56.0±3.2	51.8±3.2		64.3±3.3	53.0±4.7	
	6	53.7±4.5	54.9±5.6		59.8±2.8	51.0±1.1		56.4±2.9	58.3±8.4	
TG/HDL-C	Bsaeline	1.36±0.15	1.42±0.15	NS	1.67±0.16	1.55±0.22	NS	1.64±0.20	1.82±0.31	NS
	3	2.00±0.53	2.02±0.32		2.26±0.41	1.89±0.32		1.59±0.19	2.25±0.49	
	6	2.73±0.61 *	2.66±0.58 *		2.23±0.32	1.82±0.63		1.88±0.20	2.26±0.78	
FBS, mg/dL	Bsaeline	87.7±2.8	86.5±3.6	NS	87.0±1.6	84.0±3.1	NS	89.2±3.7	85.4±2.6	NS
	3	83.2±2.6	82.8±3.5		89.2±4.4	78.2±1.6		94.0±3.0	83.3±8.2	
	6	84.6±2.8	83.5±4.6		90.3±3.7	77.5±6.2		90.2±3.4	82.7±5.7	

Values are mean ± SE unless otherwise specified. NS = not significant, † $P < 0.05$, †† $P < 0.01$, for intragroup comparisons
* $P < 0.05$, for intragroup comparisons for each time point relative to the baseline values.
Abbreviations: BW = body weight, BMI = body mass index, TG = triglyceride, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, FBS = fasting blood glucose

Follow-Up Data and Evaluation

Metabolic measures for subjects with follow-up data are shown in Table 2.

Body weight and BMI levels were increased at 6 months from baseline in five subgroups except the aripiprazole/+VPA group, and BMI levels were significantly increased in the olanzapine/-VPA group.

TG levels were increased at 6 months from baseline in all subgroups, and significantly higher TG levels were observed in olanzapine/-VPA, olanzapine/+VPA, and paliperidone/-VPA groups.

LDL levels were increased at 6 months from baseline

in groups receiving paliperidone, and decreased in groups receiving aripiprazole, although not significantly.

HDL levels were decreased, although not significantly, at 6 months from baseline in groups receiving olanzapine.

The TG/HDL-C ratios were increased at 6 months from baseline in all subgroups, and significantly increased in olanzapine/-VPA and olanzapine/+VPA groups.

Within the paliperidone/+VPA, aripiprazole/-VPA, and aripiprazole/+VPA groups, there were no significant differences in the levels of TG, LDL-C, HDL-C, or TG/HDL-C ratio at any time point after baseline.

Fasting blood glucose remained unchanged throughout the observed period in all subgroups.

No significant changes in the metabolic markers were detected between baseline and 3 months or between 3 and 6 months.

The changes over time from baseline to 6 months in body weight and TG/HDL-C ratio were separately extracted from databases, and are presented in Figure 1.

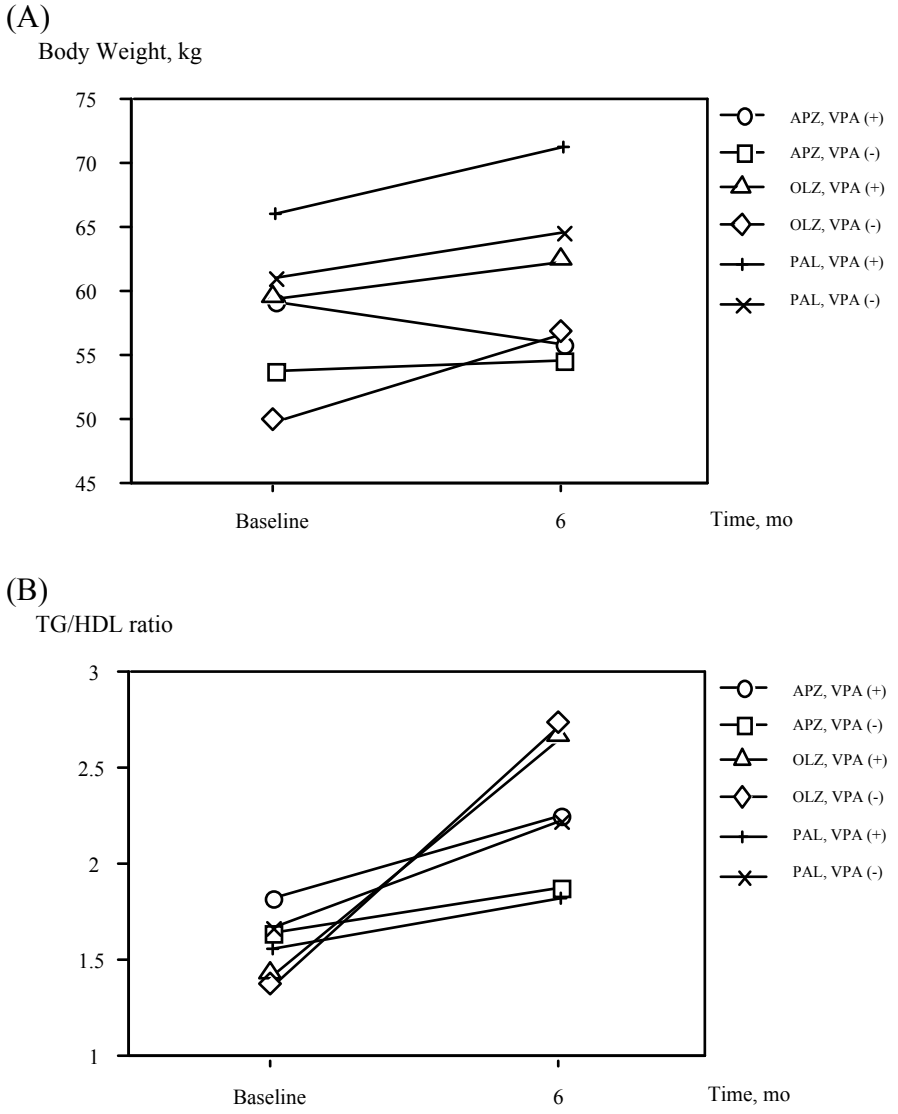

Figure 1. Changes in (A) Body Weight and (B) Triglyceride/High-Density Lipoprotein Cholesterol (TG/HDL-C) Ratio at Baseline and 6 Months

DISCUSSION

Our study demonstrates that concomitant use of VPA with atypical antipsychotics produced no additional effects on body weight/BMI compared with any atypical antipsychotic monotherapy, although differences in lipid levels and insulin resistance were observed during the 6-month study period.

Olanzapine produced greater increases in body weight and BMI and significantly higher levels in TG and TG/HDL-C ratio at 6 months. This same tendency was observed in patients who received paliperidone.

However, there were differences between the metabolic effects of the two atypical antipsychotics when VPA was used concomitantly. VPA maintained the adverse metabolic effects associated with olanzapine and inhibited those associated with paliperidone. VPA did not affect the metabolic effects of aripiprazole.

Valproate treatment has been reported to be associated with obesity [5]. Valproic acid could directly stimulate the secretion of insulin from the pancreatic β cells [3], but it has also been suggested that valproate may interfere with insulin metabolism in the liver, resulting in higher insulin concentrations in peripheral circulation [4]. In several previous studies, valproate treatment has been associated with low total and HDL cholesterol and elevated triglyceride levels [14]. One possible mechanism underlying these abnormalities is that valproic acid is a well-known enzyme inhibitor that may result in lower levels of cholesterol, and the other is that an increase in serum insulin is believed to affect lipolysis in adipose tissue and cause altered lipid as well as leptin profiles [15].

Reports have been published on the metabolic effects of atypical antipsychotics and mood stabilizers. One study has shown that the use of atypical antipsychotics and mood stabilizers is associated with disordered lipids in euthymic bipolar patients [16], and the other study confirmed that only users of atypical antipsychotics (olanzapine, quetiapine, or risperidone) had higher metabolic syndrome rates than either users of atypical antipsychotics in combination with mood stabilizers (sodium valproate and/or lithium) or users of mood stabilizers alone [17]. In another retrospective study of bipolar patients receiving risperidone, olanzapine, or clozapine as an add-on to standard mood stabilizers, weight gain was significantly greater with olanzapine (4.0 kg) than with risperidone (2.4 kg) for 4 weeks, and the combination of divalproex and atypical antipsychotics caused more weight gain than did combination therapy with lithium [18]. Casey et al. reported significantly greater mean weight gain and a decrease in LDL-C levels in patients with schizophrenia who received olanzapine plus divalproex extended-release compared to olanzapine monotherapy in a 12-week study [19]. These studies support our findings that olanzapine and VPA combination therapy transiently decreased LDL-C levels at 3 months and increased weight gain and some metabolic levels as well as monotherapy at 6 months.

A study on the metabolic effects of paliperidone compared with olanzapine found that the TG/HDL ratio, insulin resistance, and glucose sensitivity for insulin worsened significantly with olanzapine, but did not change significantly with paliperidone [20]. Meltzer et al. reported valproic acid reduced, although not significantly, the adverse effects of risperidone [21]. As paliperidone (9-OH-risperidone) is the main metabolite of risperidone, our results that VPA slightly decreased the metabolic effects of paliperidone might be consistent with this past study. Several reports had suggested that the combination of aripiprazole and valproate might present a low risk of metabolic side effects compared with other combination therapies [22, 23]. However, long-term longitudinal data evaluating the metabolic effects of these three atypical antipsychotics with or without valproate augmentation are lacking.

There is no evidence to support the premise that the metabolic effects of olanzapine or paliperidone with VPA are due to a pharmacokinetic mechanism. Concurrent use of valproic acid significantly decreases the serum concentration of olanzapine to an extent comparable to smoking [24], and valproate did not alter the concentration of risperidone or 9-OH-risperidone [25]. The changes in the metabolic outcomes associated with olanzapine or paliperidone plus VPA found in our study are likely to reflect a pharmacodynamic interaction between these atypical antipsychotics and VPA. On the other hand, there are reports of therapeutic doses of valproate having no clinically significant effects on the pharmacokinetics of aripiprazole or dehydro-aripiprazole in patients with schizophrenia or schizoaffective disorder, or in another drug-monitoring study [26, 27].

Low levels of HDL-C and elevated TG are risk factors for insulin resistance and cardiovascular disease; further, elevations of TG are associated with small LDL particles [28]. The simple, readily calculated measure of the TG/HDL-C ratio has been identified as a superior marker of insulin resistance in patients with schizophrenia as well as various other populations [29]. In this study, there were no significant differences in baseline TG/HDL-C ratio among the 6 subgroups. As it happens, this marker reflecting insulin resistance was thought to be useful for investigating changes over time in the metabolic effects of atypical antipsychotics with or without VPA.

There are several limitations to the present study. First, it was a nonrandomized retrospective study design with a limited sample size and some dropouts. Second, measured metabolic values were not adjusted for age or sex, and previous antipsychotic medications were not taken into account. Third, we assumed that a

closed-ward setting would minimize inter-individual differences in energy intake and expenditure. However, some patients were discharged because of improvement in psychotic symptoms, and it was therefore difficult to evaluate how much food intake and physical activity were controlled as outpatients. Despite these limitations, this study provides more useful information, in combination with our previous report [30], about the weight gain and lipid changes in Japanese psychotic patients who received VPA while on "representative" atypical antipsychotics in a "real-world" treatment setting.

In conclusion, VPA may produce little additional metabolic effects on top of those of olanzapine (having the strongest metabolic effect) or aripiprazole (having the weakest metabolic effect), while interfering with those of paliperidone (having an intermediate metabolic effect). Additional, prospective studies are needed on the interactions between VPA and atypical antipsychotics on metabolic effects.

ACKNOWLEDGEMENTS

The authors would like to thank our colleagues in all departments of Kusatsu Hospital for their assistance with this report. There are no conflicts of interest in this study.

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