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A Pilot Trial of Sodium Benzoate, a D-Amino Acid Oxidase Inhibitor, Added on Augmentative and Alternative Communication Intervention for Non-Communicative Children with Autism Spectrum Disorders

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Abstract

Background: This open-label clinical trial examined the efficacy and safety of a d-amino oxidase inhibitor, sodium benzoate, in the treatment of non-communicative children with autism spectrum disorder. We hypothesized that benzoate, through indirect glutamate stimulation, may enhance learning in communication.

Method: Six children (five boys, one girl, 3-year-7-month to 9-year-6-month of age) completed the 12 weeks of study of receiving sodium benzoate in conjunction with communication training program. The outcome measures were Receptive and Expressive Vocabulary Test-Chinese, parent-reported Adaptive Behavior Assessment System-II, number of core vocabularies learned in the applied communication learning system, Chinese child developmental inventory and parenting stress index. Safety assessments included biweekly recorded vital signs, body weight, body height and adverse events.

Results: We noted improvement of communication in half of the children on benzoate. An activation effect was reported by caregivers in three of the six children, and was corroborated by clinician's observation.

Conclusion: Though the data are too preliminary to draw any definite conclusions about efficacy, they do suggest this therapy to be safe, and worthy of a double-blind placebo-controlled study with more children participated for clarification of its efficacy.

Keywords: Glutamate; Autism; Clinical trial; Communication; Benzoate

Introduction

Current neuroscience researches hypothesized that autism spectrum disorders (ASD) are neurodevelopmental disorders of the neuronal synapseses with abnormal connectivities [1,2]. Molecules targeting brain dendritic spine regulation for the purpose of promoting its maturation and restoring spine stability are thus considered to be of therapeutic potential in ASD. Because glutamate and its ionotropic N-methyl-D-aspartate (NMDA) receptors have been known to be associated with synaptic plasticity, glutamate and NMDA receptors-mediated signaling have become targets of interest in exploring the pharmacological treatment of ASDs [3,4].

One possible approach is to raise synaptic concentrations of D-amino acids by reducing their metabolism by D-amino acid oxidase (DAAO) [5-7]. Sodium benzoate is a readily available DAAO inhibitor with a well-developed safety profile. Benzoic acid and its salts are generally recognized as safe food preservatives and are widely used in manufacturing fruit jelly, buffer, soybean sauce, and processed meat [8]. In addition, sodium benzoate has been approved for the treatment of urea cycle enzymopathies, which is a rare disease usually diagnosed in childhood.

As for application of benzoate for neuropsychiatric disorders, two prior clinical trials have been reported. They were respectively a double-blind, placebo-controlled trial for early-phase Alzheimer disease [9] and for schizophrenia [10]. Significant improvements in clinical symptoms, neurocognitive ability and quality of life were observed in both clinical trials. In the present study, we hypothesized that sodium benzoate could be beneficial for children with ASD due to its ability to indirectly augment the NMDA-mediated glutamertergic neurotransmission and thus may possibly enhance learning.

Methods

This study was a pilot twelve weeks open label trial with the aim of gaining preliminary experience with sodium benzoate for the treatment of non-communicativel children with ASD. The participants were a convenient sample of outpatients children recruited from the Department of Pediatrics, Kaohsiung Medical University Hospital, Taiwan.

All these children were already diagnosed as with autistic disorder by DSM-IV [11]. Before entering this study, they all received careful reassessment using DSM-5 criteria to be ascertained of meeting the ASD criteria [12]. The other inclusion criteria for participation of this study were 1) the child was currently with severe communication problem 2) the child did not receive augmented picture exchange communication system for communication 3) parents could be cooperative with the at home training requirement. For children receiving other psychiatric medication, the drugs had to be at a stable dose for at least 2 months before entering the study and remained unaltered throughout the clinical trial. Concomitant educational, occupational, physical or behavioral treatment was permitted, but no new treatment was allowed to be added except the communication training we provided in this study. The research protocol was approved by the Institutional Review Boards (Registration number: F(I)-20150003) of the hospital mentioned above.

The final participants included six children (five boys, 1 girl) with age between 3-year-7-month to 9-year-10-month old. For children with body weight equal or more than 15 kg, benzoate was given with 500 mg/day. For children with body weight less than 15 kg, benzoate was given with 250 mg/day. (Of note, the therapeutic dose of benzoate given for children with urea cycle enzymopathies is in the range of 250-500 mg/kg/per day) Sodium benzoate was provided by Excelsior Pharmatech Labs (Taiwan).

All the children entering this study also started to receive communication training using the Core Vocabulary Communication System- Chinese version (the Unlimiter Assistive Technology Engineering Lab, Taiwan). Parents were required to teach their children 40 minutes per day at home using this System. During the 12 weeks study period, the parents were required to bring children back the hospital every 2 weeks. At the baseline and the final (12 weeks) visit, the following assessments were arranged.

Receptive and expressive vocabulary test-chinese (REVT)

REVT assesses the language ability of children between 3-yah and 6-year-11-monthof age, and also for children older than 7-year-old who have language developmental delay. The Chinese version of REVT with normative data has been available since 2011 [13]. The REVT-Chinese has two parts, receptive part and expressive part. The test results are usually scores and presented as a norm-referenced standard score. However, our nonverbal participants were either not testable or completed at the floor score, thus study results are reported by two domains (i.e., receptive and expressive) in percentile achieved as compared with standardized norm.

Core vocabularies gained in the core vocabulary communication system

There are total 72 core vocabularies depicted in pictures in the Chinese Core Vocabulary Communication System, and they are tested in two ways: 1) by asking the participant to identify the pictures though "point -to-the-picture-of-the-word-I-say" technique. and 2) by asking the participant to name the individual picture. Study results are reported by the total vocabularies the child learned through the 12 weeks study period.

The Chinese child developmental inventory-chinese version (CCDI)

The Chinese Child Developmental Inventory (CCDI-Chinese) [14,15] is a 320-item parent-report measure of development which targets seven domains, i.e., gross motor, fine motor, comprehension, expressive language, situation-comprehension, personal-social and self help. An integrated domain called "General Development" was derived from the seven domains and was usually used as index for global development. Developmental Quotient (DQ) is calculated by the months obtained in General Development divided by chronological age x100. Study results are reported by pre and post DQ.

The adaptive behavior assessment system-II (ABAS-II)-Chinese version

The ABAS-II is an individually administered, norm-referenced measure of adaptive behaviors [16]. The parent provided information in the skill areas of Communication, Community Use, Functional Academics, Home Living, Health/Safety, Leisure, Self-direction and Social skills. A Global Adaptive Composite (GAC) score is calculated from all nine skill area scores and presented as a norm-referenced standard score. Study results are recorded by the pre- and post Global Adaptive Composite (GAC) score and Social score.

Parenting stress index-Chinese version (PSI)

Primary caregiver filled out the Chinese version of the parenting stress index [17] whichwas a validated Chinese version of the original questionnaire developed by Abdin [18] that measured aspects of parental functioning. The PSI parent domain scale contains 54 items and child domain scale contains 47 items. In addition to the thirteen subscales, the parent and child domains yield a total score and a derived raw-to-percentile score. As reported by the validated Chinese PSI manual, the "total stress score" used a cut-off score of 286 for the abnormal band (equivalent to derived raw-to-percentile score above 85 percentile) [17].

Clinical global impression –improvement scale (CGI-I)

The CGI-I is an observer-rated scale that measures the global improvement of illness as compared to condition at admission to the trial. The improvement is measured using a range of responses from 1 through to 7: 1) Very much improved, 2) Much improved, 3) Minimally improved, 4) No change, 5) Minimally worse, 6) Much worse, and 7) Very much worse.

Data Analysis

The case number was too small for meaningful quantitative analysis. Thus we presented the data of baseline condition and post-treatment measures by qualitative description. Please see Table 1 and the following anecdotal case summaries for the report of results.

Report of case-series

Child A was a boy diagnosed as with ASD when he was at 3-year-1-month of age. He had already received pivotal response training focusing on joint attention, individual speech therapy, behavioral training and motor training. At the time of the study entry, he was at 4-year-4-month-old and would say some the name of different kinds of cars and bulldozes. He would point to the door indicating his wish to

go out and pointed to numerical numbers while demanding parents to read them out loud. He little smiled and usually lied on the floor and pushed the car around by himself. After 12 weeks into the study, child A was considered to be much improved. At the final assessment day, he was with a smiling face, and uttered in short sentence spontaneously (e.g. saying "I do not want tea, I want water" while seeing the picture of tea). When we tested him by showing the picture of "eyes", he responded as "Eyes, I do not want the eye drop in my eyes" (referring to his experience of visiting ophthalmologist for eye infection). However, he was still not able to be engaged in reciprocal talk.

		A	B	C	D	E	F
Age		4Y4M	5Y9M	9Y6M	3Y7M	8Y7M	4Y1M
Gender		M	F	M	M	M	M
DQ	Pre-Tx	56	39	24	42	31	45
	Post-Tx	79	42	25	46	35	44
REVT-R	Pre-Tx	<1%	<1%	<1%	x	x	
%	Post-Tx	32%	<1%	<1%	x	<1%	
REVT- E	Pre-Tx	<1%	<1%	<1%	x	x	
%	Post-Tx	24%	3%	<1%	x	x	
CV- I	Pre-Tx	55	50	45	x	16	0
(total number)	Post-Tx	72#	72#	45	x	42	21
CV-N	Pre-Tx	42	49	31	x	4	0
(total number)	Post-Tx	72#	72#	37	x	46	18
ABAS-GCS	Pre-Tx	77	60	47	53	50	58
	Post-Tx	77	61	46	49	53	57
ABAS-S	Pre-Tx	71	51	57	61	46	45
	Post-Tx	77	51	50	44	46	45
PSI	Pre-Tx	70	97.5*	99*	99*	69	50
%	Post-Tx	62	93*	99*	99.9*	75	72
CGAS	Pre-Tx	40	40	40	21	40	40
	Post-Tx	60	51	40	21	50	40
CGI		much	much	minimal	nil	much	minimal

Table 1: Characteristics and outcome measures of the subjects.

Note: DQ: developmental quotient derived from the Chinese Child developmental inventory, X: not able to be tested, REVT-R: Receptive and Expressive Vocabulary Test-receptive part, results are reported in percentile achieved as compared with standardized norm, REVT-E: Receptive and Expressive Vocabulary Test-expressive part, results are reported in percentile achieved as compared with standardized norm, CV-I: core vocabularies the child can identity in the pictures of Communication System by pointing (maximal as 72, marked as #), CV-N: core vocabularies the child can identity in the pictures of Communication System by pointing (maximal as 72, marked as #), ABAS-GCS: Parental reported General Adaptive Composite Score from Adaptive Behavior Assessment System-II, ABAS-S: Parental reported Social Score from Adaptive Behavior Assessment System-II, PSI: parenting stress index , * is marked when the derived raw-to-percentile score is above 85 percentile, CGAS: Children's Global Assessment Scale, CGI: Clinical Global Impression-Improvement.

Child B was a 5-year-9-month-old girl with non-communicative speech when she entered the trial. She was diagnosed as with ASD when she was at 3-year-8-month of age. At the baseline, she would have repeated sentences with no meaning for the context and was not able to be engaged in reciprocal conversation. She was always in a happy mood, but would become irritable when her preferred daily routines were disrupted. During the study, child B had mastered all the core vocabularies, and gradually whispered some of the picture naming task. Her parents noticed obvious increase amount of her speech and her being more willing to accept prompt and correction. We concluded child B to be much improved in this clinical trial.

Child C was a 9-year-6-month-old boy with limited words when he entered the trial. He could say the name of several food items to indicate his need, but no other meaningful phrases could be expressed. He would keep repeating "twenty seconds, twenty seconds" to himself when he was alone. Child C was diagnosed as with ASD when he was at 2-year-6-month of age. Due to limited communicative ability, he c was put in special class from grade 1. He also received psychiatric medication of methyphenidate and risperidol from the age of 6-year-9-month due to labile mood, irritability, restlessness and poor sleep, and the doses were unaltered since the age of 8-year-3-month. After entering the study, the only obvious gain was for him to be familiar with the name of the days (e.g. Monday, Tuesday, Wednesday...). At the final assessment day, the only answer he could reply promptly was to the question of "What day is today?" In addition, in the first 3 days of benzoate usage, he was not able to fall asleep at his usual sleep time, albeit the night time medication of risperidal usage was unaltered. Mother reported that he would stay awake in bed and mumbled incomprehensible sounds in a self-soothing way for one hour more. We concluded child C to be of minimal improvement.

Child D was a 3-year-7-month-old boy who was diagnosed as with ASD when he was at 1-year-8-month of age. He had received pivotal response training on joint attention. At the baseline, child D had no meaningful words and was with high activity level. He kept running and sliding on the floor or climbing up and down. At the final assessment day, child D showed no improvement. He still had no meaningful word, and showed no interest in the training pictures, communication board and talking pen. He was quite happy all the time and his activity level became even higher. Constant adult supervision was needed to keep him from danger due to excessive running. His sleep pattern was unaltered.

Child E was a 8-year-4-month-old boy who could only say simple phrase (e.g. "Eat cookie", or "wait a minute") under strong maternal insistence. He was diagnosed as with ASD when he was at 3-year-6-month of age. Due to limited communicative ability, he was put in special class from grade 1. After entering the study, child E showed interest in using the talking touch pen and communication board from

the very beginning. He became more willing to increase the length of his utterance by copying parental remark. The self-talking at home also increased. At the 56 days on the trial, he could say "Mother, I want to eat cookie". At the last visit (the 84th in study), he could whisper "how are you, doctor" under mother's prompt when we met and said "Bye-bye, doctor" spontaneously when he left. However, in the first two weeks of the study, his activity level increased. His mother described him as "always rushed in and out, climbed up and down ". The activity level gradually returned to the baseline one month later. His sleep pattern was unaltered. Child E was concluded as much improved.

Child F was a 4-year-1-month -old boy who was diagnosed as with ASD when he was at 1-year-6-month of age. At the baseline of this study he could only say the name of certain foods under strong maternal prompt. He would lie on the floor immersing in his own world by lining up toy cars, and totally ignored adult's bidding. At the end of the study, he could point and name about one fourth of the Core Vocabularies in the Communication system, but he still had no use of them. However, he was noted to manifest change in his daily home activity by increasing observation of his younger brother at play. He was no longer intensely preoccupied with his monotonous car line-up play. We concluded child F to be minimally improved.

Discussion

Our pilot study revealed that benzoate seemed to have beneficial effects in teaching of communication skill as observed by the parents and clinicians. Half of the participants (child A, B, E) were judged to be much improved. Our pilot study also revealed that benzoate seemed to have untoward activating effect in further increasing the originally high activity level of two subjects (child D, E) and affecting sleep (child C). From the literature review, we know that intentional intake of food addictive and preservatives (i.e., sodium benzoate) have been linked to increased hyperactivity in 3-year-old and 8/9-year-old children in the community [19]. Daily sodium-benzoate rich beverage consumption has also been reported to be associated with increased reporting of ADHD symptoms in college students [20]. Thus the finding of the activating effect of sodium benzoate in our children of ASD was not surprising. Nevertheless, the activity levels of these three children were not disturbing to the extent of requiring medical attention or withdrawal from the study.

Up to now, only a few glutamatergic compounds have been studied in clinical trials of ASD, and the results are inconclusive [4]. Previous experimental attempts for ASD treatment with intention of enhancing and augmenting NMDA function included molecules like D-Cycloserine (DCS), sarcosine and GLYX-13. DCS, a partial glycine B agonist at the NMDA receptor site, has been shown to improve sociability in mouse models and a small human study [21]. In recent years, DCS was shown to be effective in improving stereotypic symptoms [22] and reciprocal social ability [23] in older adolescents and young adults with ASDs. Sarcosine is a potent endogenous inhibitor of glycine transporter 1 and can enhance NMDA neurotransmission [24-26]. In an open-label trial of sarcosine for 24-week treatment of high function children with ASD, there was no significant treatment effect identified by analysis of the outcome measures. S [27]. GLYX-13 is a monoclonal antibody fragment with partial agonist effects at the glycine modulatory site. Treatment with GLYX-13 has been demonstrated to rescue the ASD-analogous behavioral deficit in the animal model [28], but no clinical trial has been reported yet. To the best of the authors' knowledge, our current small sample pilot trial is the first report documenting the effect and side effects of benzoate therapy in children with ASD.

The limitation of this study is its nature of being an open trail without placebo control group. It is difficult to judge the magnitude and validity of improvement in the absence of placebo controls. Though our data are too preliminary to draw any definite conclusions, they do suggest this therapy to be possibly beneficial and worthy of a double-blind placebo-controlled study with a focus on a certain subgroup of ASD children.

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Conflict of Interest

There are no industry-sponsored contribution nor of any corporate participation in preparing the manuscript. The authors declare no conflict of interest.

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