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Inositol treatment of autism

Short Communication

J. Levine[1], **A. Aviram**[2], **A. Holan**[1], **A. Ring**[1], **Y. Barak**[1], and **R. H. Belmaker**[3]

[1] Abarbanel Mental Health Center, Bat Yam (affiliated to the Sackler School of Medicine, Tel Aviv University), [2] Child Diagnosis and Rehabilitation Center, Edith Wolfson Medical Center, Holon, and [3] Ministry of Health Mental Health Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beersheva, Israel

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Summary. Recent studies suggest that serotonin reuptake inhibitors are helpful in at least some symptoms of autism. Inositol is a precursor of the second messenger for some serotonin receptors, and has been reported effective in depression, panic disorder and obsessive-compulsive disorder. However a controlled double-blind crossover trial of inositol 200 mg/kg per day showed no benefit in 9 children with autism. Since biochemical studies suggest that inositol may augment serotonin effects, future studies could evaluate inositol in children already receiving serotonin reuptake inhibitors.

Keywords: Autism, inositol, controlled study.

Introduction

Autism was considered in the past as a severe developmental neuropsychiatric disorder with little hope for pharmacological amelioration. Recent studies of serotonin specific reuptake inhibitors with positive benefit in autism (Gordon et al., 1992; Cook et al., 1992) have given renewed impetus to the search for effective treatments of autism. Inositol is a simple isomer of glucose that serves as a precursor for synthesis of phosphatidylinositol, the second messenger system for serotonin $5HT_2$ receptors. Rahman and Neuman (1993) showed that exogenous inositol enhances serotonin function in a rat brain electrophysiological model. We reported positive benefit of 12 gm/day inositol in double-blind, controlled trials of depression, panic disorder and obsessive-

Table 1. Demographics

Patient No	Initials	Sex F/M	Age Yrs	Age at Dx (mths)	Early* development	Mental retardation	Baseline CARS score
1	CA	M	5	18	delayed	moderate	40.5
2	GM	F	6	22	normal	moderate	32.5
3	LN	M	5	24	normal	severe	40.5
4	RL	M	5	22	normal	moderate	38.5
5	MI	M	4	15	normal	mild	33.5
6	PB	M	6	16	delayed	severe	47
7	KH	M	6	9	delayed	moderate	45.5
8	GD	M	6	27	normal	moderate	36.5
9	LA	M	6	23	normal	severe	50
10	BA	M	7	19	delayed	severe	55

*First year development as described by the child's parents

compulsive disorder (Levine et al., 1995; Benjamin et al., 1995; Fux et al., 1996). We now report a study of inositol in autism.

Methods and subjects

The study was approved by the Helsinki Committee and informed consent signed by all the participants' legal guardians. Ten children entered the study after DSM-IIIR diagnosis of infantile autism. All subjects were outpatients on unrestricted diet. There were 9 males and 1 female. Mean age was 5.6 years ± 3.2. Mean age at diagnosis was 19.5 months ± 5.2. Early development was described in medical records as "normal" in 6 of 10 and "slow" in 4 of 10. One of the subjects suffered from co-morbid epilepsy and continued to receive carbamazepine 200 mg/d throughout the study, (No 6). Routine blood count and chemistry, free-T4 and lysosomal enzyme levels were within normal limits in all subjects. Karyotype was normal in all subjects, as was CT, EEG and MRI (in two subjects). See Table 1 for demographics.

The rating instruments used for evaluation of inositol's effects and side-effects were: Childhood Autism Rating Scale (CARS) (Schopler et al., 1980), Clinical Global Impression (CGI) and the Conners Parent-Teacher Questionnaire (CONNERS) (Conners, 1969). All subjects were evaluated at baseline, 2 weeks, 4 weeks, 6 weeks and 8 weeks.

The study's duration was 8 weeks. Containers of inositol were pre-coded by one of the investigators (JL) and distributed by the blinded investigators to the subjects. Dextrose, of similar texture and taste, served as placebo. After 4 weeks the containers (inositol or dextrose), were returned to the dispensing investigator and the compound changed in a cross-over manner. Myo-inositol or placebo (dextrose) 200 mg/kg body weight was dissolved in juice in two equal daily doses.

One child (#4) refused to continue to ingest the dissolved powder after 4 weeks. At the trial's completion he was found to have been given placebo. Statistical analysis includes only the 9 subjects who completed both phases of the study.

Results

Table 2 summarized the CARS during this study. No significant statistical differences were found for the CARS, the CGI scores, or the Conners.

Table 2. CARS scores during inositol or placebo treatment

No	Placebo			Inositol		
	Baseline	2 wks	4 wks	Baseline	2 wks	4 wks
1	41.5	48	48.5	40.5	48	41.5
2	32.5	33	38.5	38.5	33	35
3	42.5	41	40	40.5	42	42.5
4	38.5	34	33.5	–	–	–
5	36.5	34	30.5	33.5	34	36.5
6	47	44	42	42	38	36.5
7	45.5	45.5	45.5	45.5	45.5	45.5
8	36.5	38	40.5	40.5	35	33
9	50	50	50	50	50	50
10	55	51	51	51	55	56
Mean	42.5	41.8	42.0	42.4	42.3	41.0
(SD)	6.9	6.7	6.8	5.5	7.8	7.6

Three of the children reported side-effects during the study. One complained of nausea, one was noticed to have a decrease in appetite and one suffered from diarrhea. All the complaints remitted spontaneously within 5 days of the study. Upon un-blinding the study codes all side-effects reported were found to have occurred during the placebo phase. No side-effects were reported during inositol treatment.

Only one child responded to the inositol treatment by a decrease in CARS from 40.5 at baseline to 33.0 after 4 weeks. This is (Schopler et al., 1980) an improvement from severely autistic to mildly-moderately autistic. He was a 5 year old boy who differed from the rest of the subjects in the fact that diagnosis of autism was established after the age of 2 years.

Discussion

Several investigators have tried to manipulate the nutrition of autistic children in order to achieve symptomatic relief. Megavitamins had no beneficial effects in autism nor did a gluten-free-diet (Zeisel, 1986). Although inositol is a natural component of diet, the present study differs form previous dietary studies since inositol has reported effects in double-blind studies of other psychiatric disorders responsive to serotonin reuptake inhibitors (Levine et al., 1995; Benjamin et al., 1995; Fux et al., 1996). Vocci and Deutch (1990) describe the need for development of novel treatments of autism. Inositol has been given safely to children (Hallman et al., 1992). Inositol augments serotonin neurotransmission (Rahman and Neuman, 1993) and serotonin reuptake blockers are effective in autism (Gordon et al., 1992; Cook et al., 1992). Thus inositol deserves further study in autism, perhaps as possible augmentation of serotonin reuptake inhibitor treatment. The CARS rating scale used in this study might not be sensitive enough to pick-up specific symptoms that could benefit from inositol, and future studies should include scales reported to be sensitive to SSRI effects in autism (Cook et al., 1992; Garber et al., 1992).

References

Benjamin J, Levine J, Fux M, Aviv A, Levy D, Belmaker RH (1995) Double blind controlled trial of inositol treatment of panic disorder. Am J Psychiatry 152: 1084–1086

Conners CK (1969) A teacher rating scale for use in drug studies with children. Am J Psychiatry 126: 884–888

Cook EH, Rowlett R, Jaselskis C, et al (1992) Fluoxetine treatment of children and adults with autistic disorder and mental retardation. J Am Acad Child Adolesc Psychiatry 311: 739–745

Fux M, Levine J, Aviv A, Belmaker RH (1996) Inositol treatment of obsessive-compulsive disorder. Am J Psychiatry 153: 1219–21

Garber HJ, McGonigle JJ, Slomka GT, Monteverde E (1992) Clomipramine treatment of stereotypic behaviors and self-injury in patients with developmental disabilities. J Am Acad Child Adolesc Psychiatry 31: 1157–4460

Gordon CT, State RC, Nelson JE, Hamburger SD, Rapaport JL (1993) A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder. Arch Gen Psychiatry 50: 441–447

Hallman M, Bry K, Hoppu K, Lappi M, Pohjavouri M (1992) Inositol supplementation in premature infants with respiratory distress syndrome. N Engl J Med 326: 1233–1239

Levine J, Barak Y, Gonsalves M, Szor H, Elizur A, Kofman O, Belmaker RH (1995) A double-blind controlled trial of inositol treatment of depression. Am J Psychiatry 152: 792–794

Rahman S, Neuman RS (1993) Myo-inositol reduces serotonin (5-HT_2) receptor induced homologous and heterologous desensitization. Brain Res 631: 349–351

Schopler E, Reichler RJ, Devellis RF, et al (1980) Toward objective classification of childhood autism: childhood autism rating scale. J Autism Dev Disord 10: 91–103

Vocci FJ, Deutsch SI (1990) Novel drug development in developmental disorders. In: Deutsch SI, Weizman A, Weizman R (eds) Application of basic neuroscience to child psychiatry. Plenum Publishing Corporation, New York

Zeisel SH (1986) Dietary influences on neurotransmission. Adv Pediatr 33: 23–47

Authors' address: Prof. R. H. Belmaker, MD, Beersheva Mental Health Center, PO Box 4600, Beersheva, Israel

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