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Lack of Benefit of Intravenous Synthetic Human Secretin in the Treatment of Autism

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The objective of this study was to determine if an intravenous infusion of synthetic human secretin improves language and behavioral symptoms in children with autism. Forty-two children with the diagnosis of autism were randomized to one of two groups in this double-blind cross-over trial. One group received 2 IU/kg of intravenous synthetic human secretin at the first visit, followed by an equal volume of intravenous saline placebo at week 6. The other group received treatments in the reverse order. All children were evaluated at weeks 1, 3, 6, 9, and 12 with standardized assessments of language, behavior, and autism symptomatology. There were no significant differences in the mean scores on any measure of language, behavior, or autism symptom severity after treatment with secretin compared to treatment with placebo. The results of this study do not support secretin as a treatment for autism.

KEY WORDS: Autism; human synthetic secretin; clinical trial.

INTRODUCTION

Autism is now recognized as a neurobiologically based disorder with a prevalence of at least 1/1000 (Bristol-Power & Spinella, 1999). The etiology remains unknown. A variety of treatments and interventions have been described, but few have been extensively researched.

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Secretin is a 27 amino acid hormone released from S cells within the proximal duodenum in response to gastric acid secretion (Ulrich, Holtmann, & Miller, 1998). In 1998, infusion of purified porcine secretin was reported to effect improvement in three children with autism (Horvath *et al.*, 1998). These patients received intravenous secretin to assess pancreatic function in the setting of intractable diarrhea (Somogyi, Cintron, & Toskes, 2000). Secretin is the primary stimulant of pancreatic ductal bicarbonate secretion, and has other biliary, intestinal, and extra-intestinal physiologic actions (Ulrich *et al.*, 1998).

Several mechanisms have been proposed for the central nervous system action of secretin that would improve language and other behaviors in children with autism. Because children with autism have gastrointestinal problems at a higher rate than the general population (Horvath, Papadimitriou, Rabsztyn, Drachenberg, & Tildon, 1999), an association between secretin receptors in the gut and those found in the hippocampal formation in the brain has been postulated (Horvath *et al.*, 1998). Animal studies have demonstrated a role

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for the secretin-vasoactive intestinal peptide-glucagon family of peptides in the stimulation of tyrosine hydroxylase activity in sympathetic nerve and in the stimulation of cyclic AMP in the frontal cortex (Fremeau, Korman, & Moody, 1986; Ulrich *et al.*, 1998). The complexities of the neurologic involvement in autism are mostly unknown, so the evidence of secretin's action on the central nervous system made the anecdotal reports of marked improvement in language and behavior biologically plausible.

An explosion of interest in secretin as a treatment for autism ensued, with multiple Internet sites devoted to its use and availability. Many children with autism received secretin before more formalized research studies were developed.

Sandler *et al.* reported the first double-blind, placebo-controlled study of human synthetic secretin (Sandler *et al.*, 1999). In this study of 56 children, significant improvement from baseline was found in both treatment and placebo groups on several items of the Autism Behavior Checklist (ABC) and the Clinical Global Impression speech score. There was no difference between groups, indicating that secretin did not contribute to the observed improvement in the study participants.

Owley *et al.* reported no significant change in the social-communication score on the Autism Diagnostic Observation Schedule–Generic or any other objective measures of communication or social interaction after a single infusion of porcine secretin in a randomized, double-blind, placebo-controlled study of 20 children (Owley *et al.*, 1999). Similar findings were reported from two other double-blind cross-over trials of a single dose of porcine secretin (Chez *et al.*, 2000; Coniglio *et al.*, 2001).

In the largest study to date, involving 95 children, Dunn-Geier *et al.* employed a randomized, double-blind, placebo-controlled design to determine the effects of a single dose of porcine secretin on language and autistic behaviors. There were no statistically significant differences between the treatment group and the placebo group on the Preschool Language Scale–3 or on measures of autism symptom severity (Dunn-Geier *et al.*, 2000).

The children who were initially reported by Horvath *et al.* (1998) had global improvement in language and the symptoms of autism. Our study was designed to measure change across several domains following treatment with synthetic human secretin (Somogyi, Cintron, & Toskes, 1999). The goal was to have a battery of standardized assessments comprehensive enough to detect any change that occurred in language ability, cognitive ability or severity of the behavioral symptoms of autism.

EXPERIMENTAL METHODS

The study was approved by the Institutional Review Board of the Children's Hospital Medical Center, Cincinnati, Ohio.

Subjects

Children were eligible for this study if they were 2–15 years of age and met the criteria for autism as outlined in the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, fourth edition (1994) following a multidisciplinary evaluation. Children not evaluated at our center were accepted into the sampling frame if documentation of diagnosis by a multidisciplinary team was sufficient as determined by a developmental pediatrician (SS).

Two hundred eighty-seven families contacted our center to volunteer to participate in this study. From the 287 families, 124 children met these initial eligibility criteria. The study was not formally advertised and was made known to our clinic population by word of mouth. Inquiries came from a five-state region, most following news media reports of improvement subsequent to the use of secretin in patients with autism.

Children were excluded from the study if they had known chromosomal or other genetic disorders, if there was a structural abnormality on neuroimaging, or if they had previously received secretin. Children were also excluded if they had acute or chronic pancreatic disease or a medical condition that might make participation in the study unsafe.

The study was designed to have 25 participants per group. Anticipating a drop-out rate of 25% in a study involving such a large commitment on the part of the family, 68 potential participants were randomly chosen from among the sampling frame of 124. These children were evaluated by the study team to confirm the diagnosis of autism and verify that the children had never been treated with secretin. Of these 68, 6 had previously received secretin and 2 were determined not to have autism.

Informed, written consent was provided by a parent or legal guardian. After 42 participants completed the study, an interim analysis was performed to ascertain whether or not significant treatment differences existed. This was done because some families who had been assigned to a later start date had either changed their minds about participation or had sought secretin outside the study, making them ineligible. The interim analysis indicated that the magnitude of the treatment differences was not sufficient to warrant continuation

of the study. The final sample sizes were 23 in group AB and 19 in group BA. One child in group AB did not return for the final visit.

At the time of first infusion, participants were randomly assigned to one of two groups: AB or BA. Group BA received secretin infusion first, followed by saline placebo infusion 6 weeks later. Group AB received these in the reverse order. Demographic characteristics of the two groups are presented in Table I. Researchers, participants, and caregivers were blind to the treatment condition. Participants received either 2 IU/kg synthetic human secretin (ChiRhoClin, Inc., Silver Spring, MD) or the same volume of saline placebo according to the randomization table in the research pharmacy. For treatment with secretin, vials containing 16 μg synthetic human secretin, 1.5 mg cysteine hydrochloride, and 20 mg mannitol were reconstituted with 8 ml normal saline by the research pharmacist. Participants received an initial test dose of 0.1 ml of the assigned treatment (typically 0.2 μg human synthetic secretin).

Assessments

Participants were evaluated on five occasions: at baseline prior to first infusion, at week 3, at week 6 prior to the cross-over infusion, and at weeks 9 and 12. Each evaluation took place in the same room and included a battery of objective, standardized assessments. The Childhood Autism Rating Scale (CARS) (Schopler, 1988), the Gilliam Autism Rating Scale (GARS) (Gilliam, 1995), and the Developmental Test of Visual Perception (Hammill, Pearson, & Voress, 1993) or selected tests of the Merrill-Palmer Scale (Stutsman, 1981) were administered by a clinical psychologist (AK). Parents were asked to complete the Aberrant Behavior Checklist (Aman & Singh, 1994) and the Autism Behavior Checklist (ABC) (Krug, Arick, & Almond, 1980) which were interpreted by the psychologist.

Receptive language skills were evaluated by a team of two speech and language pathologists (JB, DM) using the Peabody Picture Vocabulary Test–3 (PPVT) (Dunn & Dunn, 1997) and the Receptive Language Scale of the Mullen Scales of Early Learning (Mullen, 1995).

Table I. Baseline Demographics by Group

	AB	BA
N	23	19
Male (%)	20 (87)	17 (89.5)
Age [mean ± SD (months)]	80.7 ± 30.7	83.5 ± 32.4
Caucasian (%)	17 (74)	15 (79)

Expressive language abilities were also assessed at each visit using a 15-min videotaped sample of spontaneous language during play with a caregiver. All utterances occurring during the 10-min sequence from minutes 2 through 12 were transcribed by a trained observer blinded to treatment status. These transcriptions were analyzed using the Systematic Analysis of Language Transcriptions software (SALT v6.0) produced by the Waisman Research Center, University of Wisconsin, Madison. A mean length of utterance (MLU) and type-token ratio (TTR) were determined for each child. The MLU is a measure of average length of spontaneous utterances of all kinds, and the TTR is a specific measure of functional vocabulary (Shipley & McAfee, 1992).

Parents were asked at each visit about stool patterns. Parents were also asked about intercurrent illnesses, medical problems and medications, and adverse events. Clinical laboratory evaluation obtained before each infusion and at week 12 included serum chemistry profile of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphorus, cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, alkaline phosphatase, γ-glutamyl transpeptidase, total protein, albumin, amylase, lipase, and complete blood count.

STATISTICAL ANALYSIS

Analyses were performed using the SAS statistical package, version 6.12 (SAS Institute, Inc., Cary, NC). The scores on the various tests were considered to be continuous variables. The statistical methods used were *t* test and analysis of covariance using PROC MIXED. Using the *t* test, variables measured at the baseline were compared in the two groups to determine if there were differences prior to the study. The design of the study was a cross-over, thus the model in MIXED contained the terms treatment, period, and visit. The baseline for each child was used as a covariate.

The cross-over design allowed each child's response to secretin to be compared to his or her response to placebo. Using this design with a sample of 42, at $\alpha = .05$, the power to detect a clinically significant change of 6 in the GARS was 81%. The power of the study to detect an effect of 10 in the Mullen Receptive Language Scale raw score, at $\alpha = .05$, was 87%.

Analysis of variance was used to determine if stool pattern or age affected response to secretin. There were not enough participants in the study to determine group differences by gender or race.

RESULTS

Aggregate results of the five evaluations are presented in Table II. There were no significant differences between the groups at baseline. Within each group, there were no significant differences in the mean scores on measures of autism symptom severity, cognition, or receptive or expressive language after treatment with secretin compared to placebo. When results across groups were pooled to analyze for treatment effect, there were still no significant differences.

Table III is a record of each participant's change from baseline following secretin and following placebo for representative tests of symptom severity and language. For consistency, the inverse of the change on the GARS and CARS was used so that positive numbers always represent improvement in score. No child showed consistent improvement across domains following secretin compared to placebo.

Secretin did not have a significant effect on stool patterns. Twenty-four (57%) of the children were reported by their parents to have loose to watery stools at the beginning of the study. These children were equally divided between groups BA and AB. Of the 12 children in group BA who received secretin first, 3 were reported to have improved stool consistency following secretin.

Table II. Measures of Autism Symptom Severity, Cognition, Receptive and Expressive Language at Baseline and Subsequent Visits: Group Mean (Standard Deviation)

	Group	Visit #1 baseline infusion 1	Visit #2 week 3	Visit #3 week 6 infusion 2	Visit #4 week 9	Visit #5 week 12	p^*
CARS[a]	AB[b]	39.2 (5.6)	37.1 (4.9)	38.3 (5.2)	37.7 (4.8)	38.6 (5.0)	.91
	BA	40.2 (5.0)	40.1 (4.8)	39.2 (4.3)	39.5 (5.2)	40.2 (4.9)	
GARS[c] Autism Quotient	AB	98.6 (9.2)	95.9 (7.8)	94.9 (8.3)	96.6 (8.2)	94.9 (8.3)	.44
	BA	102.0 (7.9)	99.8 (8.7)	98.1 (7.8)	97.5 (8.1)	98.1 (8.4)	
Merrill-Palmer Scale	AB	30.1 (34.6)	40.3 (35.7)	36.3 (35.6)	38.4 (34.7)	40.1 (34.8)	.71
	BA	22.1 (28.5)	26.0 (31.5)	25.7 (31.6)	24.6 (33.4)	29.5 (39.6)	
Mullen Receptive Language	AB	18.5 (11.5)	19.3 (11.4)	20.3 (10.9)	21.6 (11.2)	21.1 (11.0)	.73
	BA	18.3 (10.5)	18.2 (10.2)	19.0 (10.1)	19.7 (9.8)	19.5 (10.4)	
PPVT[d]	AB	13.3 (25.1)	15.7 (23.2)	15.9 (26.6)	17.1 (24.6)	16.9 (27.3)	.55
	BA	10.0 (22.4)	13.7 (28.7)	15.4 (26.6)	15.7 (25.9)	14.2 (24.1)	
MLU[e]	AB	1.06 (1.04)	1.06 (1.03)	1.24 (1.24)	1.1 (1.15)	0.94 (1.07)	.15
	BA	1.10 (1.09)	1.03 (1.16)	1.20 (1.28)	0.97 (1.23)	0.82 (1.11)	
TTR[f]	AB	0.45 (0.41)	0.45 (0.37)	0.30 (0.32)	0.43 (0.36)	0.31 (0.30)	.94
	BA	0.42 (0.41)	0.36 (0.39)	0.36 (0.39)	0.26 (0.32)	0.22 (0.31)	

[*] p value for treatment effect for pooled data on all 42 subjects.
[a] Childhood Autism Rating Scale.
[b] AB = placebo followed by secretin; BA = secretin followed by placebo.
[c] Gilliam Autism Rating Scale.
[d] Peabody Picture Vocabulary Test.
[e] Mean Length of Utterance.
[f] Type-Token Ratio.

Table III. Change in Score from Baseline Following Secretin Treatment and Change from Baseline Following Placebo

	GARS Autism Quotient		CARS		Mullen Receptive Lang		MLU	
ID #	Secretin	Placebo	Secretin	Placebo	Secretin	Placebo	Secretin	Placebo
1	0	0	5.0	1.0	1	3	0.03	−0.16
2	0	3	8	−3.5	4	−2	−0.33	−0.14
3	−6	6	3	10	2	−2	—	0
4	6	−3	−1	−2	−2	0	0	0
5	15	−9	−3	−2.5	0	0	−0.25	−0.73
6	−3	−3	4.5	3.0	3	4	—	0
7	2	8	1.0	3.0	0	1	0.05	−0.51
8	2	0	−1.5	1.5	−7	5	0.21	−0.61
9	9	−6	−2.0	−0.5	−2	2	0	0
10	−12	3	2.5	−1.0	1	5	0	0
11	−4	9	−3.0	4.5	2	−3	−1.33	−1.0
12	−18	6	−5.0	0.5	1	−1	1.17	1.0
13	0	4	−4.5	3.0	−3	−2	−0.04	−1.36
14	6	6	2.5	3.0	3	1	0	0
15	2	−4	0.5	1.0	−1	0	0.03	0.01
16	−8	0	−2.0	1.5	3	−4	0.44	−0.5
17	−18	−2	−4.0	3.0	0	5	−0.5	−0.33
18	3	3	1.0	−1.0	−1	6	—	—
19	8	6	−2.0	0.5	0	3	0.43	0.17
20	−2	−9	7.0	4.5	−2	4	−0.36	−0.26
21	−3	6	0.5	4.5	4	0	0	0
22	0	0	1.0	1.0	−3	2	−0.44	−0.26
23	−9	9	4.0	1.5	0	6	−1.36	0.43
24	9	3	1.5	3.0	3	0	0	−1.0
25	−9	2	7.5	3.5	9	3	0.62	2.55
26	3	12	−3.0	5.0	−2	2	0	1.0
27	0	13	0.5	0.5	−2	−4	−0.91	0.06
28	0	3	−5.5	−5.0	−1	0	1.0	0
29	9	−3	4.0	−1.5	0	2	0	0
30	0	6	−5.0	−6.0	−2	−2	0	0
31	0	0	−2.5	−0.5	1	2	−1.5	−2.0
32	−4	−3	2.5	−0.5	−1	−1	−1.0	0.10
33	−3	3	0	1.0	−1	3	−0.33	0
34*	—	3	—	−0.5	—	11	—	—
35	0	3	0	6.0	−1	−2	0	0
36	6	−3	−1.5	−0.5	−1	2	0	0
39	8	8	6.0	1.0	0	0	1.09	1.14
40	0	6	−4.5	0.5	0	−2	0.3	0.33
41*	6	—	−1.0	−4.0	6	−1	0	0
42	−2	0	1.0	3.0	5	8	−0.38	0.12
43	3	1	1.05	3.0	8	—	1.0	−1.0
44	−3	12	−1	2.5	5	0	1.5	0

*Not included in final analysis

5 following placebo. In group AB, receiving placebo first, 4 had a reported improvement in stool consistency following secretin, 3 following placebo. There were no significant differences on any of the standardized tests in response to secretin between the group with loose stools and the group with normal stools.

One child had worsening of constipation during the course of the study. Six of the participants had mildly elevated AST levels at the first visit, which remained stable throughout the study. Transient elevations of AST occurred in five other children. Three children had slightly elevated amylase and/or lipase levels, which remained stable.

At week 12, parents were asked which infusion they thought contained the active secretin. They were correct exactly 50% of the time.

DISCUSSION

Reports from clinical trials have shown improvement in language and behavioral symptoms in both secretin and placebo groups, attributed to "placebo effect" (Sandler *et al.*, 1999). There have been no significant differences between the groups. With a comprehensive battery of assessment tools, we also found no significant difference between secretin and placebo treatment.

Comparisons across studies are made difficult by the lack of uniform standardized measurements of change in this population. A meta-analysis performed by Dunn-Geier *et al.* included subjects from their own study and those children studied by Sandler and Chez (Dunn-Geier *et al.*, 2000). Each of these studies had a different definition of a positive response, with emphasis on either language improvement or improvement in behavioral symptoms.

A limitation of all studies of individuals with autism is the heterogeneity of this population, even among those diagnosed using the strictest clinical criteria. The sample in this study may not be representative of the population of children with autism. Many families self-referred to this clinical trial in an effort to secure secretin treatment for their child.

The ratio of male to female participants was 8:1, twice the ratio commonly cited in prevalence studies of autism (Bryson, 1996). A similarly skewed ratio was present in other clinical trials of secretin, 7:1 (Chez *et al.*, 2000) and 12.6:1 (Dunn-Geier, 2000). This sample characteristic may be the result of a referral bias. The overrepresentation of boys in these samples warrants further investigation into a clinical difference between boys and girls that may have led parents of boys to seek out study participation at higher rates.

This was a fixed dose study of human synthetic secretin. With this report, 298 children have been given a single dose of either porcine or human synthetic secretin within a published research protocol without clear evidence of an effect. The question of whether or not multiple doses would produce an improvement remains unanswered.

The anecdotal reports of significant improvements that were carried by the national news media reached a large and receptive audience. We had an overwhelming number of requests for the medication and continue to receive inquiries about it.

The controlled studies of secretin, including this one, had sufficient power to detect a change as large as that described by Horvath (Horvath *et al.*, 1998). These studies have uniformly found no such improvement attributable to secretin. At $300 per treatment, the expense is significant, and the potential long-term effects of either porcine or human synthetic secretin are unknown, weighting the cost-benefit ratio heavily against the use of secretin.

As more is learned about the interconnections of the gastrointestinal and central nervous systems in children with autism, secretin may yet play a role. However, its use as an intravenous treatment for the language and behavioral symptoms of the disorder cannot be recommended on the basis of the research findings.

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REFERENCES

Aman, M., & Singh, M. (1994). *Aberrant Behavior Checklist—Community*. East Aurora, NY: Slosson Educational Publications, Inc.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed). Washington, D. C.: Author.

Bristol-Power, M. M., & Spinella, G. (1999). Research on screening and diagnosis in autism: A work in progress. *Journal of Autism and Developmental Disorders, 29*(6), 435–438.

Bryson, S. E. (1996). Brief report: Epidemiology of autism. *Journal of Autism and Developmental Disorders, 26*, 165–167.

Chez, M. G., Buchanan, C. P., Bagan, B. T., Hammer, M. S., McCarthy, K. S., Ovrutskaya, I., *et al.* (2000). Secretin and autism: A two-part clinical investigation [In Process Citation]. *Journal of Autism and Developmental Disorders, 30*(2), 87–94.

Corigho, S. J., Lewis, J. D., Lang, C., Burns, T. G., Subham-Siddique, R., Weintraub, A., *et al.* (2001). A randomized, double-blind, placebo-controlled trial of single-dose intravenous secretin as treatment for children with autism. *Journal of Pediatrics, 138*(5), 649–655.

Dunn, L., & Dunn, L. (1997). *Peabody Picture Vocabulary Test*. Circle Pines, MN: American Guidance Service.

Dunn-Geier, J., Ho, H. H., Auersperg, E., Doyle, D., Eaves, L., Matsuba, C., *et al.* (2000). Effect of secretin on children with autism: A randomized controlled trial. [In Process Citation]. *Developmental Medicine and Child Neurology, 42*(12), 796–802.

Fremeau, R. T., Jr., Korman, L. Y., & Moody, T. W. (1986). Secretin stimulates cyclic AMP formation in the rat brain. *Journal of Neurochemistry, 46*(6), 1947–1955.

Gilliam, J. E. (1995). *Gilliam Autism Rating Scale.* Austin, TX: Pro-ed.

Hammill, D., Pearson, N., & Voress, J. (1993). *Developmental Test of Visual Perception* (2nd ed.). Austin, TX: Pro-Ed.

Horvath, K., Papadimitriou, J. C., Rabsztyn, A., Drachenberg, C., & Tildon, J. T. (1999). Gastrointestinal abnormalities in children with autistic disorder [see comments]. *Journal of Pediatrics, 135*(5), 559–563.

Horvath, K., Stefanatos, G., Sokolski, K. N., Wachtel, R., Nabors, L., & Tildon, J. T. (1998). Improved social and language skills after secretin administration in patients with autistic spectrum disorders. *Journal of the Association for Academic Minority Physicians, 9*(1), 9–15.

Krug, D., Arick, J., & Almond, P. (1980). *Autism Behavior Checklist.* Austin, TX: Pro-Ed.

Mullen, E. M. (1995). *Mullen Scales of Early Learning.* Circle Pines, MN: American Guidance Service.

Owley, T., Steele, M., Corsello, C., Risi, S., McKaig, K., Lord, C., *et al.* (1999). A double-blind, placebo-controlled trial of secretin for the treatment of autistic disorder. *Medscape General Medicine/journal/1999/v01.n10.*

Sandler, A. D., Sutton, K. A., DeWeese, J., Girardi, M. A., Sheppard, V., & Bodfish, J. W. (1999). Lack of benefit of a single dose of synthetic human secretin in the treatment of autism and pervasive developmental disorder [see comments]. *New England Journal of Medicine, 341*(24), 1801–1806.

Schopler, E. (1988). *The Childhood Autism Rating Scale.* Los Angeles, CA: Western Psychological Services.

Shipley, K., & McAfee, J. (1992). *Assessment in Speech-Language Pathology.* San Diego, CA: Singular Publishing Group.

Somogyi, L., Cintron, M., & Toskes, P. P. (1999). Synthetic human secretin compared to synthetic porcine secretin in pancreatic function testing [abstract]. *Pancreas, 19,* 439.

Somogyi, L., Cintron, M., & Toskes, P. P. (2000). Synthetic porcine secretin is highly accurate in pancreatic function testing in individuals with chronic pancreatitis. *Pancreas, 21*(3), 262–265.

Stutsman, R. (1981). *Merrill-Palmer Scale of Mental Tests.* Wood Dale, IL: Stoelting Co.

Ulrich, C. D., II, Holtmann, M., & Miller, L. J. (1998). Secretin and vasoactive intestinal peptide receptors: Members of a unique family of G protein-coupled receptors. *Gastroenterology, 114*(2), 382–397.