Effects of Intravenous Secretin on Language and Behavior of Children With Autism and Gastrointestinal Symptoms: A Single-Blinded, Open-Label Pilot Study

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ABSTRACT. *Background.* **Autism is a severe developmental disorder with poorly understood etiology. A recently published case series describes 3 autistic children with gastrointestinal symptoms who underwent endoscopy and intravenous administration of secretin and were subsequently noted by their parents to demonstrate improved language skills over a 5-week period. This report sparked tremendous public interest, and investigators at several sites moved quickly to design controlled trials to test the efficacy of secretin as a therapy for autistic children. However, this is the first effort specifically designed to replicate the initial reported findings in terms of patient age, presenting symptoms, and drug administration.**

Objective. **To rigorously apply the scientific method by assessing the reproducibility of the reported effects of intravenous secretin on the language of young children with autism and gastrointestinal symptoms.**

Methods. **We performed a single-blinded, prospective, open-label trial by conducting formal language testing and blinded behavioral rating both before and repeatedly after a standardized infusion of secretin. We selected autistic children who were similar in age and profile to those described in the published retrospective case review. Inclusion criteria for study participation included age (3–6 years), confirmed diagnosis of autism, and reported gastrointestinal symptoms (16 had chronic diarrhea, 2 had gastroesophageal reflux, and 2 had chronic constipation). Twenty children (18 male) were admitted to the Pediatric Clinical Research Center at the University of California, San Francisco after administration of the Preschool Language Scale-3 (PLS-3). A 3 CU/kg dose of secretin (Secretin-Ferring) was administered intravenously (upper endoscopy was not performed). Behavioral ratings were derived using the Autism Observation Scale applied to a 30-minute time sample of the child's behavior consisting of a videotape of the PLS-3 (structured setting) and a second free play session with a standard set of developmentally appropriate toys. Participants then returned for follow-up evaluations, with readministrations of the PLS-3 at 1, 2, 3, and 5 weeks' postinfusion, and videotaping of each session for later blinded review by 2 independent observers using the Autism Observation Scale, uninformed about week of posttreatment. We also surveyed parents of our study children about their impressions of the effects of secretin using a 5-point Likert scale for parents to rate changes seen in their child.**

Results. **With a total study completion rate across all participants of 96%, repeated measures analyses of variance revealed no significant increases in children's language skills from baseline across all 5 study time periods after a single infusion of secretin. Similarly, neither significant decreases in atypical behaviors nor increases in prosocial behaviors and developmentally appropriate play skills emerged. Furthermore, no relationship was found between parental reports of change and observable improvement in the sample. Despite the objective lack of drug effect, 70% of parents in our study reported moderate to high change in their child's language and behavior. Furthermore, 85% of parents reported that they felt that their child would obtain at least some additional benefits from another infusion of secretin.**

Conclusions. **The results of our pilot study indicate that intravenous secretin had no effects in a 5-week period on the language and behavior of 20 children with autism and gastrointestinal symptoms. The open-label, prospective design of our study with blinded reviews of patients both before and after secretin administration follows the scientific method by seeking to reproduce an observed phenomenon using validating and reliable outcome measures. Pilot studies remain a mandatory step for the design of future randomized, clinical trials investigating potential treatments for children with autism.** *Pediatrics* **2001;108(5). URL: http://www.pediatrics.org/cgi/content/full/108/5/e90;** ***autism, intravenous secretin, gastrointestinal symptoms, children.***

ABBREVIATIONS. PDD, pervasive developmental disorder; GI, gastrointestinal; IV, intravenous(ly); UCSF, University of California, San Francisco; PLS-3, Preschool Language Scale-3; AOS, Autism Observation Scale.

Autism is a severe behavioral syndrome of unknown cause that presents with a loss of developmental milestones and speech at around 2 years of age. By *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria, autism represents an extreme form of pervasive developmental disorder (PDD), but children may have PDD without meeting all criteria for autism.[1] Therapeutic options for autism have been advanced in the past with little overall impact on the disease. Certain current treatments for autism are considered palliative but not curative.[2]

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Anecdotally, children with autism have been reported in the past to suffer from a variety of gastrointestinal (GI) symptoms, although no clear association between autism and the GI tract has ever been identified. [3] In 1998, Horvath et al[4] described 3 autistic children (ages 3, 4, and 5) with chronic diarrhea who underwent upper GI endoscopy. During endoscopy, a porcine form of the hormone secretin (Secretin-Ferring) was administered intravenously (IV) to test pancreaticobiliary function. Although no pancreatic dysfunction was demonstrated, within 5 weeks of undergoing testing, parents of all 3 patients reported increased expressive language and eye contact. The dramatic improvements in autistic symptoms were attributed to the single dose of secretin, leading the authors to speculate about a possible role for IV secretin in children with autism.

As the pharmaceutical agent in question, secretin is currently indicated for single use in adults for the diagnosis of pancreatic exocrine disease or gastrinoma. Secretin has no known therapeutic effects. No data are available on safety and efficacy in children of either the porcine-derived or available human synthetic forms.

Secretin is not the only biological or nonbiological agent to be prematurely heralded as a potential breakthrough for children with autism. [5] Nevertheless, Horvath's description of the off-label use of secretin, and its unexpected reported therapeutic effects sparked widespread public interest, perhaps facilitated by rapid dissemination across the Internet. Within weeks of its publication in January 1998, multiple anecdotal reports had appeared on Web sites and in chat rooms. Shortly thereafter, a major seminar was organized and attended by leaders in autism,[6] and a prime-time television program ("Dateline NBC", October 8, 1998) aired, all focusing on children with autism who were reported by their parents to have benefited from IV secretin. By August 1999, autism interest groups were reporting via the Internet and at public forums that >4000 affected children had received secretin treatments, with claims of improvement in >70% of recipients.[7]

In response to ensuing public demand, several research groups investigated the efficacy of secretin as a treatment for autism.[8–10] In particular, Sandler et al[8] published a placebo-controlled randomized clinical trial of 60 children ages 3 to 14 (mean age of 8) years with diagnoses of PDD, including autism. The children in the Sandler study were given human synthetic secretin and followed for 4 weeks. Although secretin treatment did not result in changes in the study children's behavior and language compared with placebo, Sandler's report left ajar several important issues.

The first and foremost question that results from the Sandler study is whether or not a subgroup of young autistic children with GI symptoms might be more predisposed to respond significantly to secretin. [11] A second issue is whether adequately sensitive measures were used that can detect subtle changes in autistic symptoms.[12] Furthermore, the Sandler study used human synthetic secretin, rather than the previously described porcine derivative, leaving open the question of whether the porcine-derived hormone might be effective.[13] Finally, the study power of the Sandler report may not have been adequate to test the hypothesis.[14]

To formally answer these questions, it seems necessary to observe the basic principles of scientific method by prospectively investigating the reproducibility of the reported effects of a single dose of IV secretin on autistic children by performing an open-label trial. [15] The data from such a trial will statistically support or refute the hypothetico-deductive process that was first used by Horvath and others to link improvements in autistic symptoms to the secretin infusion.

We recreated the conditions of the Horvath report by investigating children of the same age with GI symptoms and a confirmed diagnosis of autism. We also used porcine-derived secretin in our trial, rather than the newer human synthetic form, and followed patients for 5 weeks after infusion to follow the time frame of the Horvath study.

Our study was intended to provide data to plan subsequent randomized clinical trials. Our study power was designed to generously detect previously described effects of secretin (changes in language and behavior) and to determine the study power that would be required for future placebo-controlled trials.[16] As study endpoints, we used a standardized language scale, parental reports and two blinded reviewers to provide validated evaluations of the children's autistic symptoms. Specifically, we sought to determine if the IV administration of exogenous secretin is associated with improvements in the behavioral symptoms and the language development of autistic children with GI symptoms as Horvath previously reported.[4]

METHODS

An open-label trial of secretin was conducted over a period of 5 weeks. Clinical measures included language and behavioral assessments at: 1) baseline (preinfusion; T1), 2) 1 week post (T2), 3) 2 weeks post (T3), 4) 3 weeks post (T4), and 5) 5 weeks postinfusion (T5). Children between the ages of 3 and 6 years of age with a previous diagnosis of autistic disorder with parental complaints of GI symptoms were considered to meet criteria for inclusion in the study. Inclusion criteria were designed to closely replicate patient presentation and protocol in the Horvath report.[4]

Potential participants were excluded from participation if they: 1) had previous treatment with secretin in any form, 2) had previous GI surgery, 3) received daily oral or injected medications other than standard multivitamins, 4) had a history of febrile seizure disorders, or 5) had incomplete immunization histories.

Participants were randomly selected from a joint database maintained by the Division of Pediatric Gastroenterology and Nutrition and the Pervasive Developmental Disorders Clinic, Child and Adolescent Psychiatry at the University of California, San Francisco (UCSF). This database consisted of approximately 1500 queries made to one or the other unit following recent media coverage of secretin. The potential subject list was initially narrowed to those meeting inclusion criteria. Participants were randomly selected by picking names from a hat and were then contacted for participation. Contacts were further interviewed by phone to ensure that inclusion criteria were met and that each family agreed to the study design (ie, travel to UCSF 5 times over a 5-week period). The study was approved by the UCSF Committee on Human Research and by the UCSF Pediatric Clinical Research Center. Informed consent was obtained from parents of all children.

Sample Size and Justification

Twenty children were selected for participation in the study. This sample size was designed to allow the investigators to exclude varied response rates based on blinded psychiatric evaluations. Responses were defined as a 20% or greater improvement in scores on several standard psychiatric measures of autism, including the Preschool Language Scale-3 (PLS-3) and 10 minute segments of standardized play. The null hypothesis to be tested was that mean differences in language and behavior scores across time would not be more than that indicated by chance. If the rate of improvement were 5% or less, secretin would not warrant additional study. If at least 3 patients out of 20 showed a response to secretin, the null hypothesis would be rejected. This sample size and rule was designed to allow for 82% power to detect a secretin response rate of at least 21% and improvement on language and observational measures with a type I error rate of <0.07 (1-tailed). The study sample consisted of 18 boys and 2 girls with a mean age of 5 years.

Measures

Children's language level was assessed using the PLS-3. This instrument is designed to assess language skills in young children from 2 weeks of age through 6 years, 1 month. The PLS-3 is subdivided into 2 subscales: 1) Auditory Comprehension and 2) Expressive Communication. Children are required to follow verbal directives using simple toys and to respond to test questions presented visually and verbally. A variety of reinforcement procedures were used to elicit cooperation from participating children. These ranged from tangible food items or brief time with a toy to social praise. Reinforcements were selected based on parent report and individual child preferences. Both subscales were administered to all children. Raw scores were used, because 85% of children achieved scores below the floor of the instrument.

Behavioral ratings were derived using the Autism Observation Scale (AOS)[17] applied to a 30-minute time sample of the child's behavior consisting of a videotape of the PLS-3 (structured session) and a second free play session with a standard set of developmentally appropriate toys. The AOS is a highly sensitive instrument for measuring autism, as it addresses a wide scope of disorder-specific behaviors. Twenty-three AOS items were grouped along 6 subscales. These included: 1) Relating (responsiveness to adults present, ability to initiate and maintain rapport, spontaneity, and eye gaze); 2) Attention/Perseveration (ability to attend, concentration); 3) Communication/Language (communicative intent, nonverbal communication, predominant communicative mode, prosody, intelligibility, pragmatics, atypical language use, echolalia); 4) Object-directed Behaviors (repetitive and sensory use of objects, unusual object use, concrete play); 5) Sensory/Motor (gross motor hyperactivity, activity level, stereotypic body movements, staring); 6) Affect (degree of positive affect, negative affect and irritability). Internal consistency was determined to be acceptable at 0.83.

Study Design

At T1, children and parents reported to the UCSF Autism Clinic for baseline language and behavioral measures. Afterward, all children were brought to the UCSF Pediatric Clinical Research Center, where full physical and neurologic examinations were performed and IV access was attained. Secretin, in a standardized dose of 3 CU/kg that is similar to high dosing used in Food and Drug Administration-approved pancreatic stimulation testing, was then administered IV gradually over 1 to 5 minutes. Children continued to be observed as inpatients for 24 hours. No adverse events resulted from the secretin infusions.

Language and behavioral measures were repeated at T2 to T5. PLS-3 protocols were scored after each time. AOS behavior observations were rated by 2 independent raters previously trained in using the instrument: a graduate student in psychology and a developmental pediatrician. Raters were blinded to the time sample viewed. Intraclass correlation revealed interrater agreement to be at 0.9.

The AOS was subdivided into 6 content areas, as described previously. Items within each grouping were scored on a scale of 1 to 3, with 1 indicating that attribute or behavior was pervasive and 3 indicating that behavior or attribute was not displayed. Thus, lower scores indicate a greater degree of impairment or atypical behavior for developmental level.

In addition to empirical measures, a parent questionnaire was administered at T3, consisting of 10 items that are listed in their entirety in Table 3. Each item was rated on a 5-point Likert scale. The parental questionnaire was designed to ascertain parents' perceptions of change following secretin infusion.

RESULTS

The study sample consisted of 18 boys and 2 girls with a mean age of 5 years. Each child was evaluated a total of 5 times. Of our 20 participants, 4 children missed 1 evaluation each, leading to a total study completion rate across all participants of 96%.

Of the 20 participants, 16 were reported to have chronic loose stools or diarrhea, 2 had diagnoses of gastroesophageal reflux, and 2 were chronically constipated.

Table 1 displays demographic descriptive data (chronological age, mental age) for the sample as well as baseline language and behavioral data.

Repeated measures analyses of variance were used to analyze children's language and behavioral scores across the 5 time periods. This procedure was selected to maximize power and examine trends by reducing within-subject variability and controlling for dependence among observations. Results are presented in Table 2.

Analyses revealed no significant increases in children's language skills from baseline following a single infusion of secretin. Similarly, neither significant decreases in atypical behaviors nor increases in prosocial behaviors and developmentally appropriate play skills emerged. Children seemed to gain an

TABLE 1. Baseline Demographics and Language and Behavior Data

	Mean	Standard Deviation	Minimum	Maximum
Age (mo)	59.5	11.4	36	73
Mental age (mo)	29.9	15.6	5	55
PLS-3 auditory comprehension (raw score)	14.9	10.5	4	37
PLS-3 expressive communication (raw score)	11.9	9.9	1	36
Behavioral ratings				
Relating	6.7	2.5	5	13
Attention/perseveration	3.8	1.4	2	6
Communication/language	15.6	2.5	11	21
Object-relatedness	6.1	1.5	3	9
Sensory/motor	10	1.6	6	10
Affect	4.5	1.2	2	6

TABLE 2. Language and Behavioral Scores Before and After a Single Secretin Infusion

	T1 Preinfusion	T2 1 Week Postinfusion	T3 2 Weeks Postinfusion	T4 3 Weeks Postinfusion	T5 5 Weeks Postinfusion	*F* (4, 16)	*P* Value
PLS-3 auditory comprehension (raw score)	14.9	15.5	16.8	16.9	16.4	0.99	NS
PLS-3 expressive communication (raw score)	11.9	12.5	13.3	13.7	13.4	1.5	NS
Behavioral ratings							
Relating	6.7	6.8	7.1	6.9	7.1	0.78	NS
Attention/perseveration	3.8	3.7	3.8	3.6	3.8	0.71	NS
Communication/language	15.6	15.8	15.8	15.5	15.6	0.44	NS
Object-relatedness	6.1	6.0	6.1	5.4	5.6	1.2	NS
Sensory/motor	10	10.1	10.2	10.1	9.9	0.38	NS
Affect	4.5	4.5	4.5	4.5	4.6	0.45	NS

NS indicates not significant.

average of 1.5 raw score points in both auditory comprehension and expressive communication on the standardized language measure. It is important to note that these gains represent raw score point increases, which remain within the same percentile range relative to normative performance. Practice effects and increased familiarity with the testing administrators and environment may also account for improved performance across time, although a unitary linear trend is not seen in these data either. When blind raters reviewed the videotaped sessions, improved communicative performance was not evident and remained relatively stable, validating the PLS-3 findings.

Finally, parent perceptions of child improvement were examined. Parents were asked to respond to 10 items indicating changes or improvements seen in their child. Items were rated on a 5-point Likert scale ranging from 1 ("not at all") to 5 ("very much"; Table 3).

No relationship was found between parental reports of change and observable improvement in the sample. Thirty percent of parents in our sample indicated very little or no change in their child, while the remaining 70% reported moderate to high change. Of note is the finding that 85% of parents reported that they felt that their child would obtain at least some benefits from another infusion of secretin. Not surprisingly, parents reporting significant changes were more likely to believe that a second infusion would be beneficial (F (1,18) = 37.19, $P < .001$).

DISCUSSION

The purpose of this study was to determine the reproducibility of reported effects of secretin as a treatment for children with autism and GI symptoms. The study was designed to provide data that would be required for the potential design of subsequent controlled clinical trials in this population. A multidisciplinary team of pediatric gastroenterologists, neurologists, psychiatrists, and statisticians participated in this project to maximize the yield of the investigation.

Our study was limited by its single-blinded, open-label design. However, this limitation reflects the fact that our team felt that it would be premature to ensure an adequately designed randomized, control trial without first reproducing the reported effects. The open-label, prospective design of our study with blinded reviews of patients both before and after secretin administration follows accepted scientific method by seeking to reproduce an observed phenomenon using validating and reliable outcomes measures.[15] In turn, the results of our pilot study indicate that IV secretin had no effects in a 5-week period on the language and behavior of a deliberately targeted sample of children with autism and GI symptoms.

The results of our study also indicate that the

TABLE 3. Parental Perceptions of Child Improvement*

	Response Missing	Not at All	Very Little	Somewhat	More Than Average	Very Much
My child's behavior has changed since infusion.	10	10	25	35	5	15
My child has been more calm since infusion.	10	10	20	45	10	5
My child has been more attentive since infusion.	10	10	10	30	30	10
My child has had more regular bowel movements.	10	20	0	40	20	10
My child has had less gastrointestinal symptoms.	10	15	25	30	10	10
I have been given more positive feedback from teachers.	10	20	15	25	15	15
My communication with my child has improved.	10	15	5	35	10	25
My child's ability to communicate with me has improved.	10	15	10	40	5	20
Eye contact has improved.	10	25	10	25	15	15
My child would benefit from another dose of secretin.	10	0	5	20	15	50

* Table shows percentage of parents' response at each choice using the 5-point Likert scale (1 = "not at all", to 5 = "very much").

majority of parents noted changes in their children's behavior. Although it is possible that the instrument used in our study to ascertain parental perceptions was too broad in scope, it is nevertheless clear that parents were also overwhelmingly in favor of repeating the dose of secretin in their children. This pattern of parental response is consistent with previously published observations by others,[8] and underscores the need for carefully designed trials of any putative therapeutic agent suggested by empirical or anecdotal evidence. The finding that most parents believed that additional infusions would be appropriate despite 30% reporting little or no changes in their child may be because of contemporary reports that single infusions may not be sufficient.

We calculated our sample size to generously design our study to ascertain small effects on a minimal number of study participants. The fact that not 1 of 20 participants in our study showed any improvement indicates that future randomized, clinical trials will require in excess of 60 participants to definitively evaluate the possibility that secretin positively affects some children with autism as compared with placebo. On the other hand, as supported by the principles of the scientific method, the increasingly converging evidence that secretin does not lead to improvements in autistic symptoms diminishes the justification for additional investigation in this area.

The Horvath report is not the first to suggest a possible link between impaired GI function and autism. In particular, lymphoid nodular hyperplasia of the terminal ileum, mild colitis, mild duodenitis, and altered intestinal permeability have been purported to be more prevalent in autistic than nonautistic populations.[4,18,19] Furthermore, malabsorption syndromes and pancreatic insufficiency have been proposed as common entities in autistic children,[20] and have led some investigators to call for focused GI clinical investigation in this population. A possible gut-brain connection that may underlie autism and other neurodevelopmental diseases may still warrant additional investigation.

In our study, we prospectively determined the reproducibility of previously reported effects of secretin in children with autism and GI symptoms. Like all studies that have followed from the Horvath report, the significance of our study continues to lie in its potential to provide valuable information about the utility of secretin to many unfortunate families affected by autism who are anxious to pursue any possible means of improving their children's symptoms.

Our study illustrates that pilot studies remain a mandatory step for the design of future randomized, clinical trials investigating potential treatments for children with autism.[15] Secretin is not the first, and will not likely be the last, unproven "cure" that captures the public's imagination. Therefore, the lessons of secretin for parents, health care providers, and scientists alike do not end with this pharmaceutical. Instead, it will be equally important to rigorously apply appropriate scientific method to the study of future treatments for autism that are certain to emerge as enthusiasm for secretin wanes.

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