Repeated Doses of Porcine Secretin in the Treatment of Autism: A Randomized, Placebo-Controlled Trial

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ABSTRACT. Background and Objectives. Anecdotal reports on the efficacy of secretin in autism raised great hopes for the treatment of children with this disorder. Initial single-dose, randomized, controlled trials failed to demonstrate any therapeutic effects of secretin. The present study is the first to test the outcome of repeated doses and to examine whether there is a subgroup of children who are more likely to achieve positive effects.

Method. Sixty-four children with autism (ages 2–7 years; 55 boys and 9 girls) with a range of intelligence quotient and verbal ability were randomly assigned, in a double-blind manner, to secretin or placebo groups. Children received 2 doses of placebo or porcine secretin, 6 weeks apart. Assessments were performed at baseline and 3 weeks after each injection using several outcome measures.

Results. There were no group differences on formal measures of language, cognition, or autistic symptomatology. Subgroupings based on cognitive level, the presence or absence of diarrhea, or a history of regression failed to show any significant therapeutic effects of secretin.

Conclusion. No evidence is provided for the efficacy of repeated doses of porcine secretin in the treatment of children with autism. The possible relationship between relief of biological symptoms and enhanced skill performance is discussed.

ABBREVIATIONS. GI, gastrointestinal; HSC, Hospital for Sick Children; ADI-R, Autism Diagnostic Interview-Revised; ADOS-G, Autism Diagnostic Observation Scale-Generic; PLS-3, Preschool Language Scale, III; ABC, Autism Behavior Checklist; ANOVA, analysis of variance.

Autism is a severe, life-long neurobiological disorder with high morbidity. The disorder affects virtually all areas of functioning, notably social, communicative, cognitive, and behavioral. Prevalence is estimated to be as high as 5/1000 for the full spectrum of autistic disorders and prognosis is generally poor. To date, the cause of autism remains unknown, and there is no specific medical treatment. Psychopharmacological management continues to be far from satisfactory, with no pharmacologic agent having been shown to alter the natural history of the disorder.

Against this background, recent clinical reports of a positive response to secretin in children with autism have generated widespread interest in and demand for this hormone. In 1998, Horvath et al reported an uncontrolled case series of 3 autistic children who showed marked improvements in their social and language skills after administration of secretin for an investigative gastrointestinal (GI) procedure. This report received considerable media attention and escalating claims of a potential cure for autism resulted in likely thousands of children with autism being given secretin injections.

Recently published placebo-controlled trials failed to show any effect of secretin on cognitive, language, or behavioral measures, suggesting that secretin is not an effective treatment in autism. It remains possible, however, that these studies may have missed clinically significant changes because of the use of a single injection (vs multiple doses), the use of human synthetic rather than porcine secretin, small sample sizes, the use of measures that may not be sensitive to drug effects, and the failure to consider possible subgroups of responders, notably those with GI symptomatology. To address these possibilities, the current study investigated the effect of 2 doses of porcine secretin in 64 children 2 to 7 years of age with autism. The primary question was whether secretin results in reliable improvements in autistic symptomatology, language, and/or cognitive functioning compared with a placebo. We also addressed the issue of possible subgroups of responders as well as possible adverse effects of multiple doses.

METHODS

Participants
Sixty-eight children (ages 2–7 years) were recruited through the Child Development Center of the Hospital for Sick Children (HSC). 64 completed the study. All children met criteria for autism or autism spectrum disorder according to the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Scale-Generic (ADOS-G); in addition, all had previously received a diagnosis of autism or pervasive developmental disor-
rater agreement on the ADI-R is excellent (0.94 – 0.97). The ADI-R consists of modules appropriate for differing levels of development and autistic symptoms; IQ differences were also examined across typically developing groups and from typically developing children. Specifically, children with autism have marked difficulty disengaging attention from an ongoing central stimulus to orient toward a newly appearing peripheral stimulus; they get stuck on the central stimulus. This task was administered at baseline and both follow-up assessments.

Parent Questionnaires
A Gastrointestinal Symptoms Questionnaire was designed for this study. At baseline, parents answered 12 yes/no questions about their child’s eating habits and GI symptoms and indicated the frequency and/or severity of existing problems in their child with autism and a nonaffected sibling. The Treatment Behavior/Side Effect Rating Scale was also developed for the current study. This parent-rated questionnaire includes behavioral (eg, irritable) as well as physiologic items (eg, rashes, diarrhea), rated on a 4-point scale ranging in frequency/severity from not at all to very much.

The Autism Behavior Checklist (ABC) was also used. This 57-item checklist of autistic behaviors is comprised of 5 subscales (Sensory, Relating, Body and Object Use, Language, and Social and Self-Help) and has good interrater reliability (0.87). Parents completed the latter 2 scales at the end of each week.

Statistical Analysis
Separate repeated-measures analyses of variance (ANOVA) were conducted to examine group (secretin; secretin vs placebo; placebo) differences on the variables of interest (ADOS-G, IQ, language scores, and number of failures to disengage attention). Separate 2 (treatment groups) × 5 (baseline, as well as 1 and 2 weeks after each injection) ANOVAs were also conducted on ABC subscale scores. Independent samples t tests were used to further explore group differences on ABC subscale scores at each of 10 weeks after baseline. To correct for multiple t tests, the significance level was adjusted as follows: P = .05/10 = .005. The data were then analyzed by subgroup (presence/absence of GI symptomatology, cognitive level, and history of regression) using 2 (treatment groups) × 2 (level of subgroup) × 2 (post 1, post 2) repeated-measures ANOVAs to test for treatment differences in language and autistic symptoms; IQ differences were also examined across GI and regression subgroups.

RESULTS
Four children did not complete the study (2 girls and 2 boys; 2 secretin and 2 placebo). One discontinued personal reasons after the second injection (secretin). One withdrew because of increased hyperactivity after the first injection (placebo), I family lost contact after the first injection (placebo), and 1 (secretin) was excluded after the final assessment be-
cause another medication was introduced during the course of the study. Thus, data were analyzed for 64 children (9 girls and 55 boys) with a mean age of 62.73 months (range: 35–92 months). Based on previous claims of considerable improvements in language,4 we anticipated an overall moderate effect size on the PLS-3. Therefore, a sample size of 64 was calculated to be sufficient to obtain power of 0.8, with α set at 0.05.21 Twenty-eight children were between the ages of 2 years 11 months and 4 years 11 months, and 36 children were between the ages of 5 years 0 months and 7 years 8 months. Eight children were enrolled while on medication (having begun at least 6 weeks before the baseline assessment): 2 were on selective serotonin reuptake inhibitors (1 secretin and 1 placebo), 2 on anticonvulsant medication (1 secretin and 1 placebo), 2 on stimulants (1 secretin, dextroamphetamine and 1 placebo, methylphenidate), 1 on melatonin (placebo), and 1 child was on ranitidine (placebo).

Participant characteristics for each group at baseline are reported in Table 1. Independent samples t tests yielded no significant baseline differences between treatment groups on Leiter-R Brief IQ12,13 scores (t = −0.72), Receptive (t = −0.3), Expressive (t = −0.49), or Total (t = 0.13) Language scores, or on autistic symptomatology, as measured by the ADOS-G (t = −0.42; all P values >.05). Based on GI questionnaire data, 3 children were reported to have reflux (1 secretin and 2 placebo) and 15 children (23%) had diarrhea, defined as 3 or more stools a day (7 secretin and 8 placebo). The incidence of diarrhea is consistent with (if not somewhat lower than) the rate reported in a larger sample of autistic children (39%) based on a questionnaire study that was conducted with a larger sample of our clinic population and will be reported separately (T. Kagan-Kushnir and W. Roberts, unpublished data). Thus, we were confident that our sample was not biased in favor of a GI-affected group.

The total sample was divided into low (standard score <70) and high IQ (standard score ≥70) based on Leiter Brief IQ (n = 53) or Vineland (n = 11): 23 children (10 secretin and 13 placebo) fell into the low IQ category, and 41 (22 secretin and 19 placebo) fell into the high IQ group. According to ADI-R criteria, 27 children (12 secretin and 15 placebo) experienced an historical pattern of regression characterized by a period of language development that included the regular and flexible use of at least 5 words (excluding mama and dada), which were subsequently lost.

ANOVA s failed to yield any significant main effects or interactions on measures of autistic symptomatology (ADOS-G, ABC) or IQ, all P values >.05. For both groups, performance increased significantly over time for Receptive (F[1.7, 94] = 4.1) and Expressive (F[1.6, 84] = 17.8; P < .05), but not Total Language score (F[1.6, 82] = 2.4; P = .1). There were no significant group effects or group by time interactions for language scores or for failures to disengage (all P values >.05).

Scores on the Relating subscale of the ABC differed significantly between groups 1 week after the first injection, with the placebo group (m = 21.08) showing less severe autistic symptomatology than the secretin group (m = 27.91; t = −3.14; P < .005).

Subgroup Analyses

Subgroupings based on presence or absence of GI symptomatology, IQ, or history of regression failed to yield significant treatment differences between subgroups on any of the measures used (all P values > .05). Data from the Side-Effects Rating Scale also failed to show any systematic relationship between secretin and improved bowel functioning, although our study was not designed specifically for this purpose.

Anecdotal Parental Reports

Although still blind to group membership, parents anecdotal ly reported the following changes: sleep improvement in 7 children (4 secretin and 3 placebo), 4 of whom had diarrhea according to the GI questionnaire (3 secretin and 1 placebo); toilet training in 2 children shortly after injection (both secretin, 1 with reported diarrhe a); night-time toileting in 3 children (2 secretin and 1 placebo); increased eye contact in 6 children (4 secretin and 2 placebo); and more connectedness in 5 children (4 secretin and 1 placebo).

Of these, only 3 children (all secretin; the first of whom had diarrhea according to the GI questionnaire) reportedly improved across several domains. The parents of one 4-year-old boy reported achievement in toilet training, solidification of stools, and improved sleep, as well as improved eye contact, socialization, and speech. Parents of another 4-year-old boy reported improved speech, awareness, and connectedness, but more aggression at school. In this child, improvement on the ADOS-G was noted initially but gains were not maintained. Parents of a 3½-year-old boy reported improved articulation, full sentences for the first time, and increased sociability.

TABLE 1. Participant Characteristics at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Secretin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (male, female)</td>
<td>32 (26, 6)</td>
<td>32 (29, 3)</td>
</tr>
<tr>
<td>Age (mo)</td>
<td>62.31 (± 14.86)</td>
<td>63.16 (± 15.87)</td>
</tr>
<tr>
<td>Percentage of cases meeting ADI-R criteria</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Regression</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Leiter IQ</td>
<td>83.05 (± 22.48)</td>
<td>77.85 (± 24.11)</td>
</tr>
<tr>
<td>PLS-3 Expressive</td>
<td>17.03 (± 8.3)</td>
<td>15.86 (± 10.28)</td>
</tr>
<tr>
<td>PLS-3 Receptive</td>
<td>20.34 (± 10.01)</td>
<td>19.48 (± 12.64)</td>
</tr>
<tr>
<td>PLS-3 Total</td>
<td>33.9 (± 7.32)</td>
<td>54.38 (± 10.88)</td>
</tr>
<tr>
<td>ABC Sensory subscale</td>
<td>16.67 (± 6.69)</td>
<td>15.14 (± 6.01)</td>
</tr>
<tr>
<td>ABC Relating subscale</td>
<td>25.33 (± 9.31)</td>
<td>23.64 (± 6.93)</td>
</tr>
<tr>
<td>ABC Body/Object Use</td>
<td>21.41 (± 10.78)</td>
<td>18.21 (± 8.13)</td>
</tr>
<tr>
<td>ABC Language</td>
<td>18.15 (± 7.28)</td>
<td>15.46 (± 7.48)</td>
</tr>
<tr>
<td>ABC Social/Self-Help</td>
<td>19.41 (± 4.39)</td>
<td>17.75 (± 2.84)</td>
</tr>
</tbody>
</table>

*Standard deviations are in parentheses. All nonfrequency values are averages.
†Including selective serotonin reuptake inhibitors, anticonvulsants, stimulants, melatonin, and ranitidine.
‡Diarrhea is defined as 3 or more stools per day.
§Regression as defined in the ADI-R.
including friendliness, a sense of humor, and eye contact, as well as hyperactivity. In all 3 children, however, there was no evidence of gains on formal clinical or psychological measures; the improvement documented on language measures did not exceed the range seen in either treatment group.

Adverse Events

The following adverse events were reported only in the secretin group and may reflect a drug effect.

- One child had a rash 1 week after the first infusion.
- One child had fever and tachycardia with vomiting within a few minutes after each injection.
- One child demonstrated possible photosensitivity.
- Three children had an increase in irritability (eg, crying, negativity, temper tantrums) starting 1 day after each injection and lasting up to 2 weeks.
- Twenty-one percent of secretin injections resulted in a generalized flushing reaction of the neck, face, and/or chest immediately after the infusion.

The following adverse events were found in both the secretin and placebo groups.

- The 3 (secretin) children with irritability also had concurrent hyperactivity (restlessness, constant movement). Two children from the placebo group were also reported to have an increase in hyperactivity. One additional child from the placebo group was reported to become so hyperactive that parents withdrew from the study, not wanting the second injection.
- Three children showed an increase in aggression (2 secretin and 1 placebo).

DISCUSSION

This study examined the effect of 2 infusions of porcine secretin on autistic symptoms and on cognitive and language measures in children with autism. Consistent with the findings from single-dose studies,5,7 double doses of secretin failed to yield significant differences between groups (secretin vs placebo) on any of the measures used. Receptive and expressive language improved in both groups, but amount of improvement did not distinguish between groups. This might contribute to the improvements reported by parents.

Although hopes had been raised for a pharmaceutical solution for children with autism, we found no evidence for the efficacy of secretin. The present study extends previous research by failing to show any positive effects for 2 doses of porcine secretin in either a large sample or in subgroups based on GI symptomatology, cognitive level, or history of regression.

ACKNOWLEDGMENTS

We thank Sasson Lavi, Milton Gold, and Michael McGuigan from the safety committee at HSC for their valuable input, and Brenda Aishford, Pat Mulcahy, Glenn Carter, Kathy Parker, and Patty Bell, the nurses in the HSC Day Care Unit, for their patience and support.

We also thank Sandy Thevarkunnel, whose contribution to the data collection was invaluable.

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*Pediatrics* 2001;107;e71

DOI: 10.1542/peds.107.5.e71

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