

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

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**SHORT TITLE:** Secretin in Autism: A Two Dose Randomized Controlled Trial

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**RUNNING HEAD:** Secretin in Autism

## 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 (aged 2-7; 55 boys, 9 girls) with a range of IQ and verbal ability were randomly assigned, in a double-blind fashion, to secretin or placebo groups. Children received 2 doses of placebo or porcine secretin, 6 weeks apart. Assessments were done at baseline and 3 weeks following 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.

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**Key Words:** autism, secretin, language, behavior, cognitive functioning, gastrointestinal (G.I.) abnormalities

## Introduction

Autism is a severe, lifelong 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,<sup>1</sup> and prognosis is generally poor.<sup>2,3</sup> To date, the etiology 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.<sup>4</sup> reported an uncontrolled case series of three autistic children who showed marked improvements in their social and language skills following 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<sup>5,6,7</sup> 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 due to the use of a single injection<sup>5,7</sup> (vs. multiple doses), the use of human synthetic<sup>5</sup> rather than porcine secretin, small sample sizes,<sup>6,7</sup> the use of measures that may not be sensitive to drug effects<sup>6</sup>, 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 with autism aged 2 to 7 years. The main question was whether secretin results in reliable improvements in autistic symptomatology, language, and/or cognitive functioning compared to a placebo. We also addressed the issue of possible subgroups of responders, as well as possible adverse effects of multiple doses.

## Method

### Participants

Sixty-eight children (aged 2-7 years) were recruited through the Child Development Centre (CDC) of the Hospital for Sick Children (HSC); sixty-four completed the study. All children met criteria for autism or autism spectrum disorder according to the *Autism Diagnostic Interview-Revised* (ADI-R)<sup>8,9</sup> and the *Autism Diagnostic Observation Scale-Generic* (ADOS-G);<sup>10</sup> in addition, all had previously received a diagnosis of autism or Pervasive Developmental Disorder (PDD) from clinicians in the community based on DSM-IV<sup>11</sup> criteria. All parents gave written informed consent for their child's participation in the study. Approval for this project was obtained from the Research Ethics Board at HSC.

### Procedure

Children were randomly assigned to secretin or placebo groups, using a random numbers table. A block randomized design was used to ensure equal numbers of children aged 2 to 4 and 5 to 7 in each group. Participants, parents and examiners were all blind to group membership. Prior to administration of the drug or placebo, participants were assessed on all medical, clinical and psychological measures (described below). Diagnoses were confirmed using the ADI-R<sup>8,9</sup> together with the ADOS-G.<sup>10</sup> The ADI-R is an investigator-directed parent interview that elicits the necessary information to make a DSM-IV<sup>11</sup> diagnosis of autism. It has been validated for use in children over 18 months of age, and yields a total score for autistic symptoms, as well as subscores for social and communicative impairments, and repetitive behaviors. Inter-rater agreement on the ADI-R is excellent (.94-.97).<sup>9</sup> The ADOS-G was used both to confirm the diagnosis and as an outcome measure during follow-up visits. ADOS-G sessions were videotaped for the purpose of assessing inter-rater reliability (reliability=83.8% on 5% of all ADOS-G assessments). Follow-up assessments were conducted 3 weeks after each injection based on the expectation from previous reports<sup>4</sup> that an effect would be most apparent at that time. These assessments included all clinical measures, except the ADI-R and cognitive testing. Cognitive measures were repeated only at the final follow-up visit. ADI-R and ADOS-G were administered by authors WR and JB who have

reliability with the University of Chicago, and then by BM and LW, who have reliability with WR and JB.

### Drug Administration

Participants were admitted to the HSC day treatment unit on two occasions, 6 weeks apart. Children fasted for 3 hours prior to intravenous injections of porcine secretin or placebo. Injections were administered by a physician not participating in assessments or data analysis. In order to minimize the likelihood of parents guessing group membership (i.e., possible unblinding), the following script was recited to all parents prior to injection: *"This infusion may cause an immediate allergic reaction. Therefore, we will first give a test dose to monitor for the reaction. If no reaction occurs after one minute, it is safe to give the full dose. The injection may also cause some temporary skin redness or flushing which may persist for a short time afterward."*

Participants first received a test dose of 0.1 ml of secretin (S) or saline placebo (P). After vital signs were taken, 2 ml/kg (0.2 ml/kg) of secretin or saline was injected. The children were monitored for 4 hours following the injection. Heart rate, respiratory rate, blood pressure, temperature and transcutaneous oxygen saturation levels were monitored. Nutritional/fluid intake and output was measured periodically. A urine sample was checked for specific gravity between 2 to 4 hours post-injection. A physician examined each patient prior to discharge.

### **Clinical and Psychological Measures**

Measures were selected based on their sensitivity to autistic symptomatology and to developmental levels of the children under study.

### Autistic Symptomatology

The *Autism Diagnostic Observation Scale-Generic*<sup>10</sup> was used to measure language, social, and behavioral features of autism at baseline and at both follow-up assessments. This scale involves direct observation of a child in a semistructured play sequence that elicits information about social relatedness

(e.g., eye contact, joint attention), play skills, verbal and gestural communication and repetitive behaviors. The ADOS-G consists of modules appropriate for differing levels of developmental and language abilities.

### Cognitive Functioning

The *Leiter International Performance Scale-Revised*<sup>12,13</sup> (Brief IQ) was used to measure nonverbal intellectual ability at baseline and final follow-up. This measure is standardized for ages 3 to 8 years and is used widely in the field. It has excellent test-retest reliability (.96), and Leiter scores are highly correlated with WISC-III scores (.85-.86). For those children unable to complete IQ testing during the study (6S, 5P); existing clinical data (i.e., Vineland Adaptive Behaviour Scales<sup>14</sup>) were used to determine level of functioning.

### Language

The *Preschool Language Scale-3rd edition* (PLS-3),<sup>15</sup> which has been validated for use with children aged 2 weeks through 6 years, 11 months, was used to provide measures of Expressive, Receptive, and Total Language functioning at baseline and both follow-up assessments. Good internal consistency of Total Language Scores is reported for the entire age range (.74 to .94). Sub-scale internal consistency ranges from .75 to .91 for children older than 1 year, 6 months. Test-retest reliability (assessed for ages 3 years to 5 years, 11 months) is excellent (range .82 to .94), as is inter-rater reliability (.89 for ages 3 years, 3 months to 6 years, 11 months).

### Visual-Spatial Attention

Performance on a simple visual orienting task has been shown to reliably distinguish children with autism from other developmentally delayed groups, and from typically developing children.<sup>16,17,18,19</sup> 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 non-affected sibling.

A *Treatment Behavior/Side Effect Rating Scale* was also developed for the current study. This parent-rated questionnaire includes behavioral (e.g., "irritable") as well as physiological items (e.g., rashes, diarrhea), rated on a 4-point scale ranging in frequency/severity from "Not at All" to "Very Much".

The *Autism Behavior Checklist (ABC)*<sup>20</sup> 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 inter-rater reliability (.87). Parents completed the latter two scales at the end of each week.

### **Statistical Analysis**

Separate repeated measures Analyses of Variance (ANOVA) were conducted to examine group (secretin; S vs. placebo; P) differences on the variables of interest (ADOS-G, IQ, language scores, and number of failures to disengage attention). Separate 2 (Treatment Groups) x 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 ten weeks following baseline. To correct for multiple t-tests, the significance level was adjusted as follows:  $p = .05/10 = .005$ . The data were then analyzed by subgroups (presence/absence of GI symptomatology, cognitive level and history of regression) using 2 (Treatment Groups) x 2 (level of subgroup) x 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; 2S and 2P). One discontinued for personal reasons after the second injection (S), one withdrew due to increased hyperactivity following the first injection (P), one family lost contact following the first injection (P), and one (S) was excluded after the final assessment because another medication was introduced during the course of the study. Data were thus analyzed for 64 children (9 girls, 55 boys) with a mean age of 62.73 months (range = 35-92 months). Based on previous claims of considerable improvements in language<sup>4</sup>, 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 .8, with alpha set at .05<sup>21</sup>. Twenty-eight children were between the ages of 2 years, 11 months and 4 years, 11 months, and 36 children fell 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 prior to the baseline assessment): 2 were on selective serotonin reuptake inhibitors (SSRIs; 1S, 1P), 2 on anticonvulsant medication (1S, 1P), 2 on stimulants (1S dextroamphetamine, 1P methylphenidate), 1 on melatonin (P), and 1 child was on ranitidine (P).

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 IQ<sup>12,13</sup> scores ( $t = -.72$ ), Receptive ( $t = -.3$ ), Expressive ( $t = -.49$ ), or Total ( $t = .13$ ) Language scores, or on autistic symptomatology, as measured by the ADOS-G ( $t = -.42$ ; all  $p$ 's > .05). Based on GI questionnaire data, three children were reported to have reflux (1S, 2P) and 15 children (23%) had diarrhea, defined as 3 or more stools a day (7S, 8P). 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 which was conducted with a larger sample of our clinic population, and will be reported separately (Kagan-Kushnir & Roberts, unpublished data). We were thus confident that our sample was not biased in favor of a GI affected group.

The total sample was divided into low ( $SS < 70$ ) and high IQ ( $SS > 70$ ) based on Leiter Brief IQ ( $n=53$ ) or Vineland ( $n=11$ ): 23 children (10S, 13P) fell into the low IQ category, and 41 (22S, 19P) fell

into the high IQ group. According to ADI-R criteria, 27 children (12S, 15P) 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.

ANOVAs failed to yield any significant main effects or interactions on measures of autistic symptomatology (ADOS-G, ABC) or IQ, all  $p$ s > .05. For both groups, performance increased significantly over time for Receptive,  $F(1.7, 94) = 4.1$ , and Expressive,  $F(1.6, 84) = 17.8$ ,  $p$ s < .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  $p$ s > .05.

Scores on the Relating subscale of the ABC differed significantly between groups one week following 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 employed, all  $p$ 's > .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

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

Of these, only 3 children (all S; 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 the third boy, aged 3-1/2 years, reported improved articulation, full sentences for the first time, increased sociability, including friendliness, a sense of humor, and eye contact, as well as hyperactivity. In all three 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:

- 1 child had a rash one week following the first infusion
- 1 child had fever and tachycardia with vomiting within a few minutes after each injection
- 1 child demonstrated possible photosensitivity
- 3 children had an increase in irritability (e.g., crying, negativity, temper tantrums) starting one day following each injection and lasting up to 2 weeks
- 21% of secretin injections resulted in a generalized flushing reaction of the neck, face and/or chest immediately following the infusion

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

- The 3 (S) 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 (2S, 1P).

## Discussion

This study examined the effect of two 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,<sup>5,7</sup> double doses of secretin failed to yield significant differences between groups (secretin vs. placebo) on any of the measures employed. Receptive and expressive language improved in both groups, but amount of improvement did not distinguish between groups, suggesting that these gains were likely due to factors such as familiarity with the testing situation, maturation, and/or ongoing behavioral interventions. We further explored our null findings by subdividing groups by GI symptomatology, cognitive level, and history of regression (any of which might reflect different underlying pathologies), and continued to find no evidence for the effectiveness of secretin.

Close scrutiny of the data from those cases for whom parents reported marked improvement failed to show any sustained clinical improvement. Further, these children did not appear to share any common characteristic such as diarrhea, which might have related to improved behaviour. The finding that language skills improved in both groups serves to underscore that at least some of our measures are sensitive to relatively subtle and short-term changes in behavior. While we cannot completely rule out the possibility that practice effects contributed to our observed gains in language performance (in both groups), language tests (such as the PLS-3), which measure children's attainment of language are less susceptible to such effects than other types of measure such as performance tasks.<sup>22</sup> We also emphasize that improvements in language have been a focus of parental reports on the effects of secretin.<sup>4</sup> Our data on language corroborate parents' observations, although the failure to show that such improvements are secretin-related underscores the importance of double-blind placebo-controlled studies.

Despite our failure to show any secretin effects in a subgroup with GI symptoms, we cannot preclude the possibility that subgroupings based on some GI measure other than diarrhea (e.g., reflux or chronic inflammation) might yield more homogeneous groups. Note further that there might be considerable heterogeneity in autistic children with bowel problems; in some there may be underlying GI

pathology, while in others the problem may be related to factors such as diet and/or anxiety. We do emphasize in this context that a large proportion of our sample was reported to have bowel, sleeping, and/or eating problems, and that these symptoms appeared to fluctuate considerably in both groups (secretin and placebo). Relief from such symptoms might be associated with enhanced capacity to function (e.g., greater compliance, more consistent skill performance, and/or a better state for learning), and might contribute to the improvements reported by parents.

While 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 two doses of porcine secretin in either a large sample or in subgroups based on GI functioning, 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 are indebted to Sandy Thevarkunnel whose contribution to the data collection was invaluable.

**Table 1. Participant Characteristics at Baseline\***

	<b>Secretin</b>	<b>Placebo</b>
N (male, female)	32 (26, 6)	32 (29, 3)
Age (months)	62.31 ( $\pm$ 14.86)	63.16 ( $\pm$ 15.87)
% cases meeting ADI-R criteria for autism/ASD	100	100
Medication (n) <sup>†</sup>	3	5
Diarrhea (n) <sup>‡</sup>	7	8
Regression (n) <sup>§</sup>	12	15
Leiter IQ	83.05 ( $\pm$ 22.48)	77.85 ( $\pm$ 24.11)
PLS-3 Expressive	17.03 ( $\pm$ 8.3)	15.86 ( $\pm$ 10.28)
PLS-3 Receptive	20.34 ( $\pm$ 10.01)	19.48 ( $\pm$ 12.64)
PLS-3 Total	53.9 ( $\pm$ 7.32)	54.38 ( $\pm$ 10.88)
ABC Sensory Subscale	16.67 ( $\pm$ 6.69)	15.14 ( $\pm$ 6.01)
ABC Relating Subscale	25.33 ( $\pm$ 9.31)	23.64 ( $\pm$ 6.93)
ABC Body/ Object Use Subscale	21.41 ( $\pm$ 10.78)	18.21 ( $\pm$ 8.13)
ABC Language	18.15 ( $\pm$ 7.28)	15.46 ( $\pm$ 7.48)
ABC Social/ Self Help Subscale	19.41 ( $\pm$ 4.39)	17.75 ( $\pm$ 2.84)

\* The following abbreviations are used in the table: ADOS-G: *Autism Diagnostic Observation Scale-Generic*; Leiter IQ: IQ derived from the *Leiter International Performance Scale-Revised*; ADI-R: the *Autism Diagnostic Interview-Revised*; PLS: the *Preschool Language Scale*; ABC: the *Autism Behavior Checklist*. All non-frequency values are averages (standard deviations in parentheses).

<sup>†</sup> Including SSRI's, anticonvulsants, stimulants, melatonin, and ranitidine.

<sup>‡</sup> Diarrhea is defined as 3 or more stools per day.

<sup>§</sup> Regression as defined in the *Autism Diagnostic Interview-Revised*.

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