Children with autistic spectrum disorders. II: Parents are unable to distinguish secretin from placebo under double-blind conditions

J Coplan, M C Souders, A E Mulberg, J K Belchic, J Wray, A F Jawad, P R Gallagher, R Mitchell, M Gerdes, S E Levy

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See end of article for authors' affiliations

Correspondence to:
Dr S E Levy, Division of
Child Development and
Rehabilitation, Children's
Seashore House of The
Children's Hospital of
Philadelphia, 3405 Civic
Center Boulevard,
Philadelphia, PA 19104,
USA;
levys@email.chop.edu

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Background: Standardised measures of behaviour have failed to detect short term improvement in children with autism following treatment with secretin. However, it is possible that standardised measures are insensitive to dimensions of child behaviour that are nonetheless detectable by parents.

Aim: To determine the ability of parents of children with autism to guess, under double blind conditions, whether their child had received secretin or placebo.

Methods: 2x2 crossover randomised blinded study, comparing the effect of synthetic human secretin 2 U/kg to placebo (saline). Sixty two children with autism (aged 43–103 months) were randomly allocated to two groups: group 1 received placebo, followed six weeks later by secretin, and group 2 received secretin followed by placebo. At the conclusion of the study, parents were asked to guess their child's group assignment.

Results: Twenty seven families guessed their child's group assignment correctly and 27 guessed incorrectly. In 48 instances, parents based their guess on perceived improvement; in six cases, parents based their guess on perceived deterioration. Six families saw no difference after either infusion, and offered no guess. One family dropped out after the first infusion, and one family was lost to follow up after the second infusion.

Conclusion: In a controlled setting, parents of young children with autism are unable to distinguish the short term behavioural effects of secretin from placebo.

Although standardised behavioural measures have failed to reveal improvement in children with autism following secretin infusion,¹ it is conceivable that standardised measures may be overlooking a key dimension of subject behaviour that is detectable by parents. Therefore, as one component of a multifaceted study of secretin in children with autism,¹ we asked parents simply to guess whether their child had received secretin or placebo, and to provide the basis for their guess.

METHODS

Participants

Subjects were 62 children with autistic spectrum disorder (ASD). Eligibility criteria and subject characteristics were as previously defined.¹

Assignment of study drug and treatment procedures

Subjects were randomised into two groups. Group 1 received saline placebo initially, followed six weeks later by human synthetic secretin (ChiRhoClin, Silver Spring, Maryland). Subjects in Group 2 received human synthetic secretin first, followed six weeks thereafter by placebo. There were no statistically significant differences between groups with respect to racial distribution, age, gender, or severity of autism. Additional details regarding methodology were as previously described.¹

At the conclusion of the study, but prior to unblinding, we asked parents to guess which infusion they believed to have been placebo, and which to have been secretin, using any criteria they wished. Here, we report on the result of these parental guesses. We also compared the parents' impressions with the results of the parental Global Rating Scale (GBRS), and delta scores on the Communication and Symbolic Behavior

Scale (CSBS) (see Rapin and Katzman² for details of these measures).

RESULTS

Results were obtained for 60 of 62 subjects (one family dropped out after the first infusion, and one family was lost to follow up after the second infusion). Twenty seven sets of parents guessed their child's group assignment correctly and 27 guessed incorrectly. Six families perceived no difference after either infusion, and offered no guess as to which infusion they believed had been secretin, and which had been placebo. There was no statistically significant association between likelihood of guessing correctly and any of the following variables: child's age, duration in study, severity of autism on the Childhood Autism Rating Scale (CARS), randomisation group, or gender.

Most parents (23/27 of those who guessed correctly, and 24/27 of those who guessed incorrectly; $\chi^2 = 0.164$, $p = 0.685$) based their guess on the perception of improvement following one or the other of the two infusions (table 2). Perceived gains included increased language, improved eye contact, and increased adaptability to environmental change. One family guessed correctly on the basis of a generalised flush following secretin infusion. Six families based their guess on the perception of deterioration following one or the other infusion, apparently reasoning that if there were any change in their child's status, then the antecedent infusion must have been secretin rather than placebo (which presumably would have

Abbreviations: ASD, autistic spectrum disorder; CARS, Childhood Autism Rating Scale; CSBS, Communication and Symbolic Behavior Scale; GBRS, Global Rating Scale

Table 1 Clinical variables and parental guesses

Feature	Guessed correctly (n=27)	Guessed incorrectly (n=27)	p value
Child's age (mth)	69	77	0.092*
Duration in study (mth)	2.78	2.82	0.090*
Autism severity (mild, moderate, severe)**	2, 13, 12	8, 10, 9	0.110**
Randomisation group (1, 2)**	16, 11	13, 14	0.413**
Gender (F, M)**	5, 22	6, 21	0.735**

*t test; NS.

** χ^2 ; NS.** Table 2** Basis for parental guesses*

	Perceived improvement	Perceived deterioration	Side effects	No perceived difference
Following secretin	23	3	1**	6
Following placebo	24	3	0	

*n=60.

**Generalised flush immediately post-infusion.

Table 3 Comparison of parents' guesses with results of standardised measures

	Guessed correctly Perceived improvement after secretin (n=23)		Guessed incorrectly Perceived improvement after placebo (n=24)	
	Mean	SD	Mean	SD
Parent GBRS				
Average on placebo	0.16	0.56	1.00	0.72
Average on secretin	0.78	0.68	0.20	0.54
CSBS				
Delta* on placebo	-0.30	6.04	2.41	9.46
Delta* on secretin	1.05	8.99	-2.12	7.61

*Delta scores = (time 2 - time 1).

had no effect on their child's behaviour). Signs of perceived deterioration cited by parents included increased hyperactivity, self stimulation, aggression, incontinence, irritability, and non-compliance. The frequency of guessing on the basis of perceived deterioration was identical among families guessing correctly and families guessing incorrectly (3/27 of each group; $\chi^2 = 0.00$, $p = 1.00$).

To compare parents' guesses with standardised measures, we examined the families who guessed correctly based on perceived improvement following secretin ($n = 23$) and the families who guessed incorrectly based on perceived improvement following placebo ($n = 24$). The single family who based a guess on cutaneous flushing, the three families who perceived deterioration following secretin, and the three families who perceived deterioration following placebo were disregarded, since the numbers of subjects in each of these groups was too small for meaningful comparison. Parental guesses were in the same direction as would be anticipated from the standardised measures (table 3): the 23 families who perceived improvement following secretin registered a higher mean score on the GBRS in the post-secretin state than the post-placebo state (0.78 versus 0.16), and a positive change in the CSBS score in the post-secretin state (1.05) versus a negative change in the post-placebo condition (-0.30). The reverse of these patterns was observed among the 24 families who perceived improvement following placebo. Therefore, our data bear out the face validity of the GBRS and the CSBS, since the results of the standardised measures were in accord with the parents' global impressions. Our study was not intended to determine whether global parental impressions would have been superior to the standardised measures. Furthermore,

although these data support the face validity of the standardised measures, they lend no support to the putative efficacy of secretin, since the likelihood of parents guessing correctly was no better than chance.

DISCUSSION

Double blind studies have failed to show benefit from short term secretin therapy. One theoretical concern, however, has been that standardised measures under controlled conditions may be insensitive to changes that are nonetheless detectable by parents in a more naturalistic home environment. By asking parents simply to guess their child's group assignment, based on whatever criteria seemed relevant to them, we minimised the risk of overlooking relevant changes that might not be captured on formal rating scales. We found that parents' ability to distinguish secretin from placebo, when permitted to use any criteria they wished, was no better than chance. In addition, we report here what we believe to be a unique finding: six sets of parents who based their guess on observed deterioration, rather than improvement—that is, a “negative placebo effect”. This negative placebo effect may be traceable to the fact that two children (not part of this study or patients at our institution) had recently been reported with seizures following infusion with secretin. We revised our consent document to include this information, and counselled parents at the time of their child's infusion regarding the low but non-zero risk of negative side effects from secretin. This information may have primed some parents to attribute deterioration to secretin. The frequency of guessing on the basis of perceived deterioration was identical among families guessing

correctly and families guessing incorrectly, suggesting that perceived deterioration was truly a placebo effect, rather than a biologically based deterioration due to secretin.

Our data support the view that placebo effect accounts for most reports of improvement following a single secretin infusion under uncontrolled circumstances. Additional factors may underlie the reported efficacy of secretin in uncontrolled settings, especially over the long term. In particular, there is a *natural history* of autism, with substantial improvement in some children over time.³ It is tempting to ascribe a child's improvement to whatever therapy he or she had been receiving at the time. At our centre, one initially eligible subject improved so much over the several months prior to actually entering the study that he was deemed ineligible by the time the study opened. Had this child received secretin in an open label setting during (or, for that matter, as part of our research protocol), he would probably have been cited as an example of the benefits of secretin.

Autism is a clinical constellation rather than a specific clinicopathological entity. Thus, it remains possible that there are individual children who derive benefit from secretin, despite the absence of statistically significant group effects. Given the weight of published findings, however, including the data we present here, it appears unlikely that secretin offers any clinical benefit to the majority of children with autism.

Summary

In a double blind crossover setting, the ability of parents of young children with autism to distinguish secretin from placebo was no greater than chance. Most parents based their guesses on perceived improvement following one infusion or the other; a minority based their guesses on perceived deterioration. The basis for parents' guesses was similar among those parents who guessed correctly, and those who

guessed incorrectly. We conclude that a single secretin infusion offers no statistically significant short term benefits for children with autism.

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Authors' affiliations

J Coplan, M C Souders, J K Belchic, R Mitchell, S E Levy, Division of Child Development and Rehabilitation, Children's Seashore House of The Children's Hospital of Philadelphia, Philadelphia, PA, USA
J Wray, State Child Development Centre, Princess Margaret Hospital, West Perth, Australia
A F Jawad, P R Gallagher, Division of Biostatistics and Epidemiology, The Children's Hospital of Philadelphia, Philadelphia, PA
M Gerdes, Division of General Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA
A E Mulberg, Division of Gastroenterology and Nutrition, The Children's Hospital of Philadelphia, Philadelphia, PA

REFERENCES

- 1 **Levy SEL**, Souders MC, Wray J, *et al.* Children with autistic spectrum disorders. I: comparison of placebo and single dose of human synthetic secretin. *Arch Dis Child* 2003;**88**:731–6.
- 2 **Rapin I**, Katzman R. Neurobiology of autism. *Ann Neurol* 1998;**43**:7–14.
- 3 **Coplan J**. Counseling parents regarding prognosis in autistic spectrum disorder. *Pediatrics* 2000;**105**(5):65 (<http://www.pediatrics.org/cgi/content/abstract/105/5/e65>).

ARCHIVIST

Cerebral haemorrhage in hereditary haemorrhagic telangiectasia

The classical triad of hereditary haemorrhagic telangiectasia (HHT, Osler-Rendu-Weber syndrome) consists of recurrent epistaxis, mucocutaneous telangiectasia, and a family history of the condition. It is an autosomal dominant condition with reported incidences in various countries of between 1 in 2500 and 1 in 8000. At least 30% of patients have pulmonary arteriovenous malformations giving rise to an increased risk of cerebral embolism and abscess. Cerebral arteriovenous malformations occur in some 10–14% of people with HHT. Presymptomatic screening for, and prophylactic treatment of, pulmonary arteriovenous malformations is widely accepted but the need for screening and prophylactic treatment is controversial in the case of cerebral arteriovenous malformations. An active approach (including neonatal screening in affected families) is more common in North America than in Europe. Now data from a large HHT clinic in London (A Eassey and colleagues. *Journal of Neurology, Neurosurgery, and Psychiatry* 2003;**74**:743–8.) have been held to justify such an approach.

The retrospective study included 674 people in 98 families; 338 had definite HHT, and 317 likely or possible HHT. Nineteen individuals did not have HHT. In all 75 strokes were recorded; 35 from definite (28) or probable (7) cerebral haemorrhage, 22 from cerebral abscess, and 18 from other cerebral embolism (abscess and embolism presumed secondary to pulmonary arteriovenous malformation). The mean age at stroke was 41 years. Under the age of 45 years the risk of cerebral haemorrhage was 23 (men) and 6 (women) times that in the general population. The risk of cerebral haemorrhage in males with HHT and a cerebral arteriovenous malformation was calculated to be similar to that previously reported in people with cerebral arteriovenous malformations but without HHT (about 2% per year). In females the rate was less than half that in males.

The balance of risks and benefits from screening and prophylactic intervention for cerebral arteriovenous malformations in people with HHT seems far from clear but the authors of this report believe that it favours an active policy. They do not say at what age screening should be done.