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

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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, 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, 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.

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.

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 Katzman 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. One family dropped out after the first infusion, and one family was lost to follow up after the second infusion.

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

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 the 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. 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 placebo was no greater than chance. Most parents based their guesses on perceived improvement following one infusion or placebo. 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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REFERENCES


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 Easey 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 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.