Simethicone in the Treatment of Infant Colic: A Randomized, Placebo-Controlled, Multicenter Trial

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ABSTRACT. Objective. To determine the efficacy of simethicone in the treatment of infant colic.

Design. Randomized, double blind, placebo-controlled.

Setting. Three general pediatric practices in distinct geographic regions.

Patients. Eighty-three infants between 2 and 8 weeks of age with infant colic.

Interventions. Treatment with simethicone and placebo in double blind crossover fashion.

Results. A total of 166 treatment periods, ranging from 3 to 10 days, were evaluated in the 83 infants. Compared to baseline, improvement in symptoms was reported for 54% of the treatment periods, worsening was reported for 22%, and for 24%, there was no change. The likelihood of the treatment period being rated as showing improvement, worsening, or no change was the same whether the infant was receiving placebo or simethicone. Twenty-eight percent of the infants responded only to simethicone, 37% only to placebo, and 20% responded to both. No statistically significant differences were noted among these three groups of responders. No difference could be shown even when infants with "gas-related symptoms" (by parental report) were separated out as a group.

Conclusion. Although both produced perceived improvements in symptoms, simethicone is no more effective than placebo in the treatment of infantile colic. Pediatrics 1994;94:29–34; colic, simethicone, infant.

Infant colic continues to be a problem for babies, parents, and physicians. Recognized since at least the sixth century, yet still defying precise understanding, colic produces variable amounts of distress for 10% to 20% of infants and their parents during the first 3 months of life.1-5 According to Carey6 research to improve the understanding and management of colic has been confounded by: 1) lack of a uniform definition of the problem; 2) poorly supported conclusions regarding its basic etiology; 3) few well-designed studies of therapy; and 4) inaccurate measurement of the amount of crying as an outcome.

From a clinical perspective, a colicky infant is typically described as an otherwise normal infant, 2 weeks to 3 months old, who fusses or screams for an extended period of time, usually in the afternoon and evening, draws his or her legs up, is largely inconsolable, and sometimes seems temporarily but inconsistently relieved by passing gas. For research purposes, Wessel's1 more specific definition of an infant with colic as, "one who, otherwise healthy and well-fed, has paroxysms of irritability, fussing or crying lasting for more than three hours a day and occurring on more than three days in any one week," has been widely accepted in the literature and was used by our group for this study.

A wide range of explanations for the cause of colic can be found in the medical literature. Allergy or intolerance to cow milk, either in the infant's or the nursing mother's diet, has its proponents and opponents.7-10

Although "maternal tension"11 has been largely discarded as a cause, problems in the interaction between the infant and the "environment" (parents)12 or, more specifically, inappropriate response(s) to the infant's crying by the parents13 are believed by some to cause or contribute to the problem. Implicit in the strategies recommended by many is the belief that colic is not a pathologic entity at all but simply an extreme variant of "normal" crying which can be caused by hunger, discomfort from a soiled or wet diaper, boredom, or from unidentifiable causes.14-16 Similarly, many interventions to prevent17 or manage colic have been reported. These range from increased carrying,18 real or simulated automobile rides,19 dietary changes for the infant or mother,7-16 counseling parents to respond "appropriately" to the crying,15,16 and medications. Dicyclomine hydrochloride has been reported as being effective21,22 but is now contraindicated in infants under 6 months because of reports of apnea in infants who were receiving it.23,24

Another agent, simethicone (methylpolysiloxane), has been promoted as being of value because of the impression that increased intestinal gas is causally associated with colic. It is advertised in professional journals as being beneficial and is often recommended by physicians who care for children. Simethicone is a defoaming agent, known to change the surface tension of gas bubbles, causing them to coalesce, and accelerates the passage of gas through the intestine although the actual volume of gas is not changed. Simethicone is not toxic, and is not absorbed from the intestine. Its safety has been well-documented.25,26

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Studies of simethicone in the treatment of colic have shown varying results. Duggan and Inchaustegui\textsuperscript{29} in both a double blind study of 20 infants and a nonblinded study of 14 infants with colic were unable to show benefit, save in two of the latter 14, where colic was "possibly improved." Danielson and Hwang\textsuperscript{28} studied 27 infants ranging from 2 to 8 weeks of age in a double blind, crossover fashion. The infants were given 0.3 cc of simethicone solution before each meal, and their responses were measured by interviews, 3-4-hour behavioral observations, and 24-hour records by parents of the infants' crying, fussing, eating, and stools. Placebo and simethicone treatments were equivalent by all measures, regardless of order of treatment, but, interestingly, the authors noted a decrease in crying during both treatment phases. This was interpreted as possible evidence for colic being self-limited and the study demonstrating the natural course of the complaint, or that a placebo effect had taken place. The authors felt that either simethicone does not in fact reduce intestinal gas, or that abdominal cramping caused by intestinal gas is not a pathogenic mechanism in infantile colic. A recent open-label study of 51 infants showed nine with symptoms resolved in 7 days, 35 improved, and seven with no improvement.\textsuperscript{30} However, neither parents nor investigators were blinded. A recent study by Sethi and Sethi\textsuperscript{31} claimed efficacy of simethicone in a randomized, double blind crossover study of 26 infants. However, colic was not defined, criteria for study entrance were not specified, the dosage used was variable, and the effective dose was not clearly described. In an earlier open-label pilot study, our group found 50\% to 80\% of 41 infants to have a positive response to administration of 0.3 ml of simethicone with feedings (unpublished data).

To determine the efficacy of simethicone for treating infant colic, we designed a study to overcome the deficiencies of earlier work. We used the generally accepted rigorous definition of colic by Wessel,\textsuperscript{1} employed a double blind, placebo-controlled, crossover format, and recruited a broad cross-section of colicky infants from several areas of the country. Additionally, we planned our study so that we could ascertain whether a subset of infants with colic, those who were felt by their parents to have symptoms suggestive of increased intestinal gas, might have a different response to simethicone from those without such symptoms.

**MATeRIALS AND METHODS**

**Patients**

Patients were recruited from three centers: University Pediatrics, the general pediatric practice of the department of pediatrics of the University of Vermont College of Medicine in Burlington, Vermont; The Pediatric Clinic of the East Carolina University School of Medicine, Greenville, North Carolina; and Willow Creek Pediatrics, a private office practice in Salt Lake City, Utah. Infants with crying sufficient to meet the criteria of Wessel's definition (see above), who were full term infants, appropriate for gestational age, between 2 and 8 weeks of age, with a weight gain of 5 ounces or more per week, and with a normal history and physical exam were eligible for entrance into the study. Infants with congenital or acquired abnormalities which might predispose them to irritability were excluded, as were infants with a prior or currently diagnosed illness or a history of treatment for hyperbilirubinemia. Possible subjects for the trial were identified during well child or sick visits; caregivers were then questioned specifically to establish whether their infants fit the above criteria for inclusion in the study. A physical exam was performed; if normal, the study consent and design were explained to the caregivers, as well as an explanation of simethicone, its hypothesized effect, and lack of side effects. Informed written consent was obtained. The Parent Questionnaire (Fig. 1) and Initial Colic Assessment Form (Fig. 2) were completed. The Daily Diary (Fig. 3) for the first trial period was explained and given to the caregiver along with the randomly selected medication for the first period. Caregivers received modest incentives (dependent on the study center) upon completion of both study periods. For example, Utah subjects received $25 cash upon completion of both study periods, and were not charged for initial or follow-up visits. The study was approved by the Institutional Review Boards of each institution.

**Study Design**

The study followed a randomized, double blind, crossover protocol, using outcome measures which could be utilized in a practice setting and permit statistical evaluation. Each patient trial consisted of two study periods of approximately 1 week each (minimum, 3 days; maximum, 10 days). Infants first received either simethicone or placebo, based on a schedule determined by random number tables, followed by the alternate substance for the second study period. Caregivers were given a bottle of coded medication and instructed to give 0.3 ml with each feeding. They were asked to record the Diaper Diary, a record of medication and to provide written comments on any events deemed noteworthy, including any modifications in dietary habits or feeding schedule. At the end of each day they were to rate their child's colic compared to when they had first sought treatment for the infant. A five-point scale was used to identify the child's symptoms as: definitely better or symptom-free (+2), possibly better (+1), the same (0), possibly worse (−1), or definitely worse (−2).

After the first study period, caregivers returned the diary and any unused medication to the physician's office, or gave it to a nurse study coordinator during a home visit. At this time, parents provided an overall response, ie, to the entire treatment period for the first medication on the same 5-point scale, ranging from +2 to −2. They were then provided with the alternative medication and a new diary. At the end of the second treatment period the diary and any unused medication were again collected, and the overall score for that period was assigned by the caregiver. If the presenting symptoms were unresolved, the child was then treated at the discretion of the physician, after discussion of the study by their caregivers at any time for any reason, and patients were dropped from the trial if an intercurrent medical condition developed.

Study medications were provided by Stuart Pharmaceuticals, then a Division of ICI Pharmaceuticals Group, and consisted of either simethicone (Mylicon Drops) or a placebo, indistinguishable in taste, smell, and appearance from Mylicon. Patient consent forms were designed at each center to conform with requirements of the respective Institutional Review Boards who approved the study at each site.

**Statistical Evaluation**

Analysis of the data was performed by statisticians from Stuart Pharmaceuticals and by an independent statistician from the University of Utah. Based on the 5-point rating scale described above an analysis of variance technique, appropriate for a crossover design, was used. Results of the two statistical analyses were identical. Daily Diaries of each patient were reviewed, scores for individual days were averaged, and these were compared to the whole number scores assigned by caregivers for each overall treatment period. Since the two sets of scores were not significantly different, the overall trial treatment period scores were used in the statistical evaluation of the results.

Simethicone "Responders" were those infants judged by their caregivers to have had a positive response (+2 or +1) only to simethicone, and no change or a negative response (0, −1 or −2) to placebo. Responders to placebo were similarly defined. For purposes of analysis the first day of the second treatment period was considered a washout period to allow the original condition
1. At what age was your baby when the problem began?

2. What is your baby drinking?
   - Breast milk
   - Formula
   - Both breast milk and formula

3. If your baby is breast feeding, are you taking any medication?
   - No
   - Yes—Please list below

4. If your baby is being fed formula, what formula are you currently using?
   Also, list any other formula you have previously used:

5. Is your baby eating any solid foods?
   - No
   - Yes—Please list below

6. Does your baby spit up after feedings?
   - No
   - Yes—Is it: 
     - Rarely
     - Often
     - Always

7. Does your baby seem to have a lot of gas?
   - No
   - Yes

8. Does your baby's stomach seem swollen, bloated, or distended?
   - No
   - Yes

9. Does your baby pass a lot of gas from his or her rectum?
   - No
   - Yes

10. Does your baby's stomach growl, gurgle or churn?
    - No
    - Yes

11. Is your baby easy to burp after feedings?
    - No
    - Yes

12. Are you able to burp your baby after every feeding?
    - No
    - Yes

13. Does burping seem to relieve his or her symptoms even temporarily?
    - No
    - Yes

14. Does passing gas from his or her rectum seem to relieve the symptoms even temporarily?
    - No
    - Yes

15. How many stools does your baby have in a 24 hour period?

16. Does your baby have trouble passing a stool?
    - No
    - Yes

17. Are your baby's stools too hard?
    - No
    - Yes

18. What have you tried to do to decrease your baby's symptoms before coming in today?

19. Are you doing any of these things now?
    - No
    - Yes—Please list below

Fig. 1. Parent Questionnaire.

to reassert itself. Ratings for that day were not included in the analysis of data. Simethicone responders were compared to placebo responders using either chi square of Student's t test depending on the variable. Patients who failed to complete the stipulated duration of both study periods were excluded from the study.

RESULTS
The study was carried out between March and August of 1988. Ninety-two patients were enrolled from the three centers. Eight were excluded for failure to keep follow-up visits. One child developed an upper respiratory tract infection and was excluded. Eighty-three patients provided data adequate for analysis. The demographic makeup of these 83 patients is shown in Table 1. Racial composition and feeding methods reflected the populations served by the three centers.

A total of 166 treatment periods were evaluated, two for each infant. Treatment periods averaged 7 days with a range of 3 to 10 days. The length of the treatment periods were influenced chiefly by logistic considerations including the parents' or the research nurses' schedules. Length of treatment period did not vary with whether the infant was receiving placebo or simethicone. As shown in Table 2, 89 (54%) of the treatment periods resulted in either definite (28%) or probable (26%) improvement of symptoms compared to baseline. Twenty-two percent resulted in definite (11%) or probable (11%) worsening of symptoms, and in 24% there was no change. Forty-one of the 83 treatment periods (25%) associated with simethicone administration and 48 (29%) of 83 associated with placebo resulted in definite or probable improvement. No significant differences were seen between simethicone and placebo treatment periods in improvement or worsening.

In Table 3, infants are divided into "Responders" (definite or probable improvement) to simethicone alone (no change or worsening with placebo), placebo alone, or those who improved with both. Twenty-three infants (28%) were termed Responders only.
COLIC ASSESSMENT FORM

<table>
<thead>
<tr>
<th>SUBJECT IDENT:</th>
<th>SEX</th>
<th>BIRTHDATE</th>
<th>ASST DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIRTHWEIGHT</td>
<td>PRESENT WEIGHT</td>
<td>INITIAL SEVERITY OF COLIC</td>
<td></td>
</tr>
<tr>
<td>ORIGIN:</td>
<td>0 WHITE</td>
<td>0 BLACK</td>
<td>0 HISPANIC</td>
</tr>
<tr>
<td>DIAGNOSES OTHER THAN COLIC</td>
<td>INONE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STUDY DRUG ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREATMENT PERIOD</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>12 = definitely better or symptom free; +1 = possibly better; 0 = same; -1 = possibly worse; 2 = definitely worse</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CONCOMITANT THERAPY</th>
<th>COMPANY USE ONLY</th>
<th>THERAPY</th>
<th>DOSE/FREQUENCY</th>
<th>FROM</th>
<th>TO</th>
</tr>
</thead>
<tbody>
<tr>
<td>(include all therapy initiated during study)</td>
<td>INONE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADDITIONAL DEMOGRAPHIC DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS PRIMARY CARE GIVER OTHER THAN PARENT(S)</td>
</tr>
<tr>
<td>_NO</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AGE</th>
<th>EDUCATIONAL LEVEL ATTAINED</th>
<th>MARITAL STATUS</th>
<th>NUMBER OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MOTHER</td>
<td>FATHER</td>
<td>CAREGIVER</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| COMMENTS |

<table>
<thead>
<tr>
<th>INVESTIGATOR'S NAME</th>
<th>INVESTIGATOR'S SIGNATURE</th>
<th>DATE (mo/da/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

to simethicone, 31 (37%) infants were termed Placebo Responders, and 17 (20%) showed improvement with both agents. Twenty-one infants (15%) showed no improvement with either agent. Analysis of the characteristics (sex, race, formula versus breast, or whether the colic was rated as mild, moderate, or severe) of those considered to be simethicone responders compared to the placebo responders showed no statistically significant differences. Evaluations of responses were done comparing infants who received simethicone in the first treatment period to those who received placebo first; no statistically significant differences were found. Finally, to test the hypothesis that simethicone would have had its greatest effect in infants whose colic was felt to be secondary to intestinal gas, the group of infants termed simethicone responders was compared to placebo responders on the basis of the caregivers answering “yes” to the questions on the Parent Questionnaire which defined a sub-group of “gassy” infants (questions 7–14, Fig. 1). The number and percentages of gassy infants in simethicone and placebo groups were not statistically different.

**DISCUSSION**

Our study is in agreement with that of Danielsson and Hwang in 27 infants in 1985.29 Both their study and ours showed that treatment with *either* simethicone or placebo produced improvement in symptoms more than twice as often as either resulted in no change or worsening of symptoms. They suggested that the improvement might be due to a tendency for colic symptoms to lessen as infants aged. Since improvement in our infants was as likely to occur during the first as during the second treatment period, and since we studied a population between 2 and 8 weeks of age, the time of increasing intensity of colic,2,3,8 the improvement we found is unlikely to be due to a natural decrease in symptoms with increasing age. A more plausible explanation is that the perceived improvement from the treatments was due to a placebo effect. This would also explain the
positive effects of simethicone noted in our earlier pilot study and in other open label studies. Different results were reported by Sethi and Sethi, who showed significant decreases in both the frequency and amplitude of daily crying spells in infants given simethicone compared to those receiving placebo. Deficiencies in their study include the lack of a clear definition of colic for study entry and a relatively small number of subjects. Simethicone would be an appealing agent to relieve the symptoms of colicky infants if it were effective. It has a very narrow range of purported therapeutic activity, ie, it reduces intestinal gas by decreasing its transit time within the gut. Moreover, being inert and not absorbed from the gastrointestinal tract, it has no dangerous side effects, an important consideration in treating a self-limited disorder. The fact that it is no more effective than placebo suggests that intestinal gas is not playing any substantial role in the symptoms of colic. Indeed, even in the infants in our study whose parents noted many symptoms of "gas," placebo was as effective as simethicone in reducing the amount of crying. The presence of "gas" may be simply a marker of colic and air swallowing rather than a cause; thus reducing gas would not be expected to provide relief. There is little data to support the notion that colic is a pathological process, or that the colicky infant is in any way abnormal, but the explanation for the excessive crying remains elusive. Fussy, crying infants may be seeking more closeness to their caregivers. Hunziker and Barr demonstrated that increasing the amount of time spent carrying infants decreased crying
TABLE 2. Effect of Treatment Number (%) of Treatment Periods Showing Change

<table>
<thead>
<tr>
<th>Agent</th>
<th>Definite Improvement</th>
<th>Probable Improvement</th>
<th>No Change</th>
<th>Probable Worsening</th>
<th>Definite Worsening</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simethicone</td>
<td>20 (12)</td>
<td>21 (13)</td>
<td>23 (14)</td>
<td>9 (5)</td>
<td>10 (6)</td>
<td>83</td>
</tr>
<tr>
<td>Placebo</td>
<td>26 (16)</td>
<td>22 (13)</td>
<td>16 (10)</td>
<td>10 (6)</td>
<td>9 (5)</td>
<td>83</td>
</tr>
<tr>
<td>Total</td>
<td>46 (28)</td>
<td>43 (26)</td>
<td>39 (24)</td>
<td>19 (11)</td>
<td>19 (11)</td>
<td>166</td>
</tr>
</tbody>
</table>

TABLE 3. Number (%) of Infants Showing Improvement to Simethicone, Placebo, or Both

<table>
<thead>
<tr>
<th></th>
<th>Definite or Partial Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simethicone alone</td>
<td>23 (28)</td>
</tr>
<tr>
<td>Placebo alone</td>
<td>31 (37)</td>
</tr>
<tr>
<td>Both</td>
<td>17 (20)</td>
</tr>
<tr>
<td>Total</td>
<td>71 (85)</td>
</tr>
</tbody>
</table>

and fussiness and increased contentment in normal infants. When employed as a treatment for colicky infants, increased carrying was ineffective. Recommendations made during prenatal and health maintenance visits that parents hold and carry their infants, explaining normal and excessive crying, and ways to respond to the crying may prevent the need for medications, formula changes, or other methods to treat well-entrenched colic later on. Being supportive and empathic as well as offering step-by-step instructions for what to do when the infant is crying along the lines suggested by Taubman are likely to be the most helpful things that physicians can do. Physicians who advise the use of simethicone, or acquiesce to its use by parents, should realize they are advocating the use of an expensive ($7.00 to $10.00 for 30 ml in Salt Lake City) placebo, albeit an apparently harmless one.

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REFERENCES
