Review of the Therapeutic Use of Simethicone in Gastroenterology

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Silicones are a large group of compounds that include large polymers containing silicon, and their properties have been employed in nanotechnology of materials and systems, even before the term was invented. Depending on the formula and the degree of polymerization and cross-linking of the polymers, they may be slippery liquids, waxes, or rubbers. Silicone oils, such as dimethicone, are currently used as excipients and in large amounts by the cosmetic and food industry as emollients, as lubricants, as thickeners and as emulsifiers for "water-in-oil" emulsions. As was shown in 'in vitro' studies [1], the surface properties of dimethicone, such as reduction of surface tension, reduction of surface viscosity and hydrophobicity, enable this substance to spread easily over a variety of substrates, assisted and accelerated by the presence of hydrophobic silica particles (SiO_2) in the simethicone (activated dimethicone) discussed herein.

The pharmacological data suggest that while simethicone (i.e. dimethicone + SiO_2) (Fig. 1) has an antifoaming effect which is 10^3 – 10^4 higher than either substance alone [2], whereas the mucosal protective effects are solely linked to the dimethicone part of the formula. As already proposed by DEBRAY [3] more than 40 years ago, simethicone appears to act as a topical barrier for protecting the mucosa against irritants such as gastric HCl, acetylsalicylic acid or biliary salts [4]. Simethicone likely acts in concert with the endogenous surface-active substances lining the gut mucosa. The effects of simethicone are those related to the intraluminal actions of the compound in the digestive tract, since it is not absorbed and is virtually non-toxic (for review, see NAIR [5]).

Background: The history of simethicone covers more than 50 years. The main properties of simethicone are the defoaming reduction of surface tension and the reduction of surface viscosity and hydrophobicity which enable simethicone to spread easily over surfaces. It is not absorbed and is virtually non-toxic. While its use is well-established in diagnostic procedures, therapeutic studies have sometimes been contradictory. **Objective:** To assess the therapeutic efficacy and safety of simethicone taking into account clinically relevant end points and following the guidelines provided by the Cochrane Collaboration. **Methods:** The data sources consulted were bibliographic databases, references from review articles and books, as well as personal contacts up to September 07. All papers were screened and those dealing with prospective clinical trials were summarized in a table by indication, study design and methodological quality. **Results:** Out of a total of 83 publications, 14 concerning diagnostic procedures and 23 therapeutic trials were retained for closer analysis. Good evidence of efficacy was found for antifoaming in diagnostic work-ups and as a therapeutic agent in: 1st) Functional dyspepsia, (4 trials; 266 patients simethicone vs. 310 controls) with simethicone superior to placebo and to cisapride, and 2nd) traveller's diarrhoea, (2 large trials; 248 simethicone patients vs. 244 placebo) with simethicone superior to placebo (increased efficacy when combined with an μ -opioid-agonist). Data are not conclusive in: 1) 'IBS-like' symptoms (2 trials; 80 patients simethicone vs. 54 controls); 2) in post-operative management of intestinal activity (4 mostly old trials; 847 patients simethicone vs. 631 controls); 3) Infantile colics, (7 trials; 306 infants simethicone vs. 296 controls); and 4) as an add-on, against symptoms of gastroesophageal reflux, (3 studies) and in partial adhesive small-bowel obstruction (1 trial). **Conclusions:** Simethicone may be beneficial in the various indications in which its intraluminal defoaming and coating action are desired. RCTs have shown its efficacy in some indications, in addition to its well-established uses in diagnostic procedures. More RCTs for non-confirmed indications are needed, particularly in view of the very large safety margin of simethicone.

Key Words: Simethicone, dimethicone, clinical review, dyspepsia, irritable bowel, diarrhoea, infant colics, endoscopy, colonoscopy

Eine Übersicht der therapeutischen Anwendungen von Simethicon in der Gastroenterologie

Hintergrund: Die Geschichte von Simethicon umfasst eine Periode von über 50 Jahren. Die wichtigsten Eigenschaften sind die entschäumende Reduktion der Oberflächenspannung, die Reduktion der Oberflächenviskosität und die Hydrophobizität, wodurch Simethicon sich rasch über Oberflächen verbreitet. Simethicon wird nicht resorbiert und ist absolut ungiftig. Während Simethicon einen festen Platz bei diversen diagnostischen Prozeduren gefunden hat, ergaben die therapeutischen Studien zum Teil widersprüchliche Ergebnisse. **Zielsetzung:** Ziel dieser Übersicht war eine Beurteilung der therapeutischen Wirksamkeit und Sicherheit von Simethicon nach klinisch relevanten Kriterien und gemäss den Richtlinien der Cochrane Collaboration. **Methodik:** Als Datenquellen dienten bibliographische Datenbanken sowie Referenzen von Übersichtsarbeiten und Büchern und persönliche Kontakte mit Experten, bis Juli 2007. Alle Publikationen wurden überprüft und diejenigen, die prospektive Studien betrafen, wurden nach Indikation, Studiendesign und methodologischer Qualität tabellarisch zusammengefasst. **Ergebnisse:** Es wurden insgesamt 83 Publikationen identifiziert; von diesen konnten 14 Studien beim Einsatz von diagnostischen Abklärungen und 23 therapeutische Studien näher analysiert werden. Die Wirksamkeits-Evidenz war "gut" bezüglich entschäumender Wirkung bei diagnostischen Eingriffen und als Therapeutikum bei: 1.) Funktioneller Dyspepsie (4 Studien; 266 Patienten mit Simethicon vs. 310 Kontrollen), wobei Simethicon sowohl Placebo wie auch Cisaprid überlegen war; 2.) Reisediarrhö, (2 grossangelegte Studien; 248 Simethicon Patienten vs. 244 Placebo) wobei Simethicon dem Placebo überlegen war (gesteigerte Wirksamkeit wenn mit einem μ -opioid-Agonisten kombiniert). Die Wirksamkeits-Evidenz war "nicht-schlüssig" bei: 1.) 'Reizdarm-artigen' Beschwerden (2 Studien; 80 Patienten mit Simethicon vs. 54 Kontrollen); 2.) Normalisierung der postoperativen Darmaktivität (4 meist ältere Studien; 847 Simethicon Patienten vs. 631 Kontrollen); 3.) 3-monats Koliken (7 Studien; 306 Säuglinge mit Simethicon vs. 296 Kontrollen); 4.) In Kombinationen bei Symptomen von gastroesophagealen Reflux (3 Studien) und bei adhäsionsbedingten partiellen Dünndarmobstruktionen (1 Studie). **Schlussfolgerungen:** Simethicon kann bei verschiedenen Indikationen bei welchen eine entschäumende und abdeckende Wirkungen erwünscht sind, von Nutzen sein. Randomisierte klinische Studien haben die Wirksamkeit von Simethicon bei verschiedenen Indikationen nachgewiesen, zusätzlich zu den gut etablierten Anwendung bei diagnostischen Abklärungen. Weitere randomisierte klinische Studien bei nicht gesicherten Indikationen sind notwendig, besonders in Anbetracht der sehr grossen Sicherheitsspanne von Simethicon.

Schlüsselwörter: Simethicon, Dimethicon, Klinische Übersicht, Dyspepsie, Reizdarm, Durchfall, Säuglingskoliken, Endoskopie, Koloskopie

Fig. 1. General formula of Polydimethylsiloxane (PDMS) or Dimethicone (+ SiO₂ = simethicone).

While its defoaming action is well established, the results of studies on the effect of simethicone on abdominal gas have been contradictory and early expectations may have been exceedingly simplistic. In an early double-blind study [6], activated charcoal, but not simethicone, significantly reduced abdominal symptoms, peak-H₂ and AUC-H₂ in expiratory breath after ingesting baked beans. In a cross-over study by Friis et al. [7,8], ten healthy volunteers were given 30 g lactulose and 600 mg simethicone or placebo. Although the end-expiratory breath samples analyzed for H₂ showed some delay and increase of the gas (e.g. AUC +19.4%, time to peak H₂ +60%) and a reduction of gastrointestinal symptoms (-41.7%), the differences were not significant. However, these trials may simply have been underpowered to detect a difference.

No pharmacokinetic interactions have been found with various drugs [9, 10] nor does it modify the urease test “in vivo” after single doses [].

The understanding of the pathophysiology of functional disorders in the digestive tract has notoriously evolved in the last 10 years [12]. Two lines of evidence caused us to review the existing evidence of therapeutic uses of simethicone:

1.) In recent years, several studies have shown that local gas formation and distension of the intestinal lumen

may be important in the pathogenesis of functional digestive disorders such as functional dyspepsia or irritable bowel syndrome. Perception of intestinal balloon distension occurred at significantly lower pressures in patients with functional dyspepsia compared with healthy controls [13]. Physiologic concentrations of intestinal lipids exert an inhibitory control on intestinal gas transit, and this mechanism is up-regulated in patients with irritable bowel syndrome (IBS) [14]. The perception of intestinal gas accumulation also depends on the mechanism of retention [15]. Patients and healthy volunteers do not react in the same manner. After 2 hours of a gas infusion, patients with irritable bowel syndrome and functional bloating alike exhibited significant gas retention, abdominal symptoms and objective distension, in contrast to healthy controls who experienced none [16].

2.) In recent years, several RCTs have reported simethicone to be effective in the management of some functional digestive disorders, to be discussed in detail below.

Methodology of the clinical review

Objective: The primary objective of the review is to assess the efficacy and safety of simethicone, from a clinical

point of view and taking into account clinically relevant end points.

Search strategy: Among the data sources consulted in the identification of trials, were bibliographic databases (TOXLINE, PaperChase browsing the databases of the National Library of Medicine and the National Cancer Institute i.e. MEDLINE, HealthSTAR, AIDSLINE and CANCERLIT, Embase, AMED, Cochrane Col.), reference lists from pertinent review articles and books, and personal contacts with experts active in the area and manufacturers up to September 2007. All papers were screened and those dealing with prospective clinical trials were retained for classification according to the selection criteria described below. In the case of double publications, the authors retained whichever was the most recent or had appeared in a peer-reviewed journal.

All trials rendered eligible were summarized in a tabulated format by one reviewer. The standard table included a full reference, a quality rating, the indication studied, demographic data and treatments, end-points (e.g. investigator's or patient's global assessments) and adverse events. The trials were grouped by indication and only those dealing with simethicone administered ‘per os’ were retained. These tables were discussed and verified with the other author until consensus was reached. No formal validation process was employed.

Selection criteria: Initially, all articles -published trials- were considered for review. These were subsequently classified by study design, screened and weighted, based on methodological quality (methods, participants, interventions, outcome measures and results).

Material scrutinised and selected: The electronic databases identified simethicone and treatment or therapy in 82 publications (n=4530 patients exposed to simethicone), i.e. 45 comparative studies; 17 additional publications were not comparative and 21 were reviews and comments. For the analysis of therapeutic efficacy, 59 studies were excluded as they were non comparative or incomplete (e.g. inadequate report of study). Twenty-

three therapeutic studies could be retained as relevant trials (see Table 2) while 14 trials dealt with diagnostic procedures (see Table 1).

Statistics: The guidelines provided by the Cochrane Collaboration Handbook for Reviews [17] have been applied in the analysis of the clinical data. The studies were tabulated and appropriate software [18] was employed in the assessment of results.

Results

Short description of pre-procedural trials

The antifoaming action of simethicone has been considered the main mechanism of action of this compound. As a direct consequence of this action, pre-treatment of patients with simethicone improves the quality of visualization by reduction of bubbles and foam in digestive ultrasonography [19,20,21] and endoscopy [22,23,24,25]; the addition of simethicone to Golytely lavage or laxatives also decreases the prevalence of colonic foam and residual stool in colonoscopy [26,27,28,29,30] and rectal ultrasonography [31] (see Table 1).

Short description of therapeutic trials

All selected studies were briefly described and the most relevant data tabulated. Thirteen comparative studies and six double-blind trials performed according to current standards were retained for closer examination. The selected studies dealt with more than 3000 patients, more than half of which were treated with the study medication, i.e. simethicone as drops or tablets. Only three trials dealing with functional dyspepsia could be included in a formal meta-analysis. In the case of infantile colics, reference was mainly made to meta-analysis conducted by other authors.

Functional dyspepsia

In spite of their popularity among patients, little attention has been paid to antifoaming agents such as simethicone in the scientific community.

Table 1. Pre-procedural simethicone, pooled results of trials

Procedure & chosen end-point	N trials	Simethicone	Placebo	Significance
Ultrasonography "improved"	4	72.0%	18.0%	P<0,001
Upper endoscopy "No additional Lavage"	2	93.9%	74.1%	P<0,001
Capsule endoscopy "good visibility"	2	70.7%	29.8%	P<0,02
Colonoscopy "No additional Lavage"	4	76.9%	48.0%	P<0,001
Rectal Ultrasonography "No artefacts"	1	90.0%	40.0%	P<0,001

The mechanisms of action of simethicone are not completely understood but there are indications that it may stimulate the smooth musculature of the upper digestive tract (HOLTMANN, 2000, unpublished data, quoted in [35]).

There are four trials including 266 patients treated with simethicone and 310 control patients in the included data-base. In an early double-blind crossover trial with 24 volunteers with a history of frequent post-prandial discomfort, the authors [32] compared the effectiveness of simethicone and placebo after a test meal. They found a significant reduction of 'bloating', 'gas' and overall preference but not significantly concerning fullness, distension, acid indigestion and pressure.

BERNSTEIN and KASICH, 1974 [33], examined whether simethicone is efficacious in the relief of functional upper gastrointestinal symptoms in a placebo-controlled trial with a fairly modern design. Patients received 50 mg simethicone or placebo. A significant decrease (P<0.001) in the severity of all symptoms combined was noted in the simethicone group (n=20) as compared with placebo (n=21). Both after 5 and 10 days, gas, fullness, bloating, distension, upset stomach, and postprandial pain were significantly less severe in the group receiving simethicone.

HOLTMANN, 1999 [34], compared the efficacy of simethicone with the prokinetic drug cisapride in patients with functional (non-ulcer) dyspepsia. After standardized diagnostic work-up including upper GI-endoscopy and at least 6-days wash-out of medication, 177 patients with functional dyspepsia were enrolled; 173 were randomized

and treated using a double-dummy technique with simethicone (84 mg t.d.s.) or cisapride (10 mg t.d.s) and a total of 166 patients completed the trial. At baseline and after 2 and 4 weeks, the intensity of the symptoms was scored from 0 (absent) to 3 (severe) using a standardized symptom questionnaire rating upper abdominal fullness, upper abdominal pain, passing of gas, early satiety, nausea, vomiting, regurgitation, heart burn, loss of appetite, perception of small or large bowel movements. Efficacy of the treatment was judged by the patients as 'very good', 'good', 'moderate' or 'no effect'. After 2 and 4 weeks, 34% and 46% respectively, of the patients treated with simethicone judged the improvement in symptoms to be 'very good' compared to 13% and 22% respectively of patients treated with cisapride (P<0.01). After 2 weeks, the difference in the improvement in the global symptom score was significantly better (P<0.001) for simethicone than for cisapride, while this difference failed statistical significance after 4 weeks (P=0.11). Interestingly, the symptom 'bloating' responded favourably to simethicone, compared to cisapride both after 2 and 4 weeks. However, at admission, there was a large proportion of females in the cisapride group (P=0.017) and a larger proportion of patients without gastric mucosal lesion in the cisapride group (P=0.039); the authors did not discuss how these differences could have affected the outcome.

In a later study, the same group [35] compared the efficacy of simethicone with placebo and cisapride in patients

Table 2. Summary of selected trials, chronologically. References are quoted in the text.

	Quality **	N Simet.	N Ref	Duration (days)	Indication	Comments
Oswald, 1961	2	40	14	variable	IBS-like	Combination
Gibstein, 1971	2	755	537	3	Post-Op.	double-blind & open
Westphal, 1972	2	13	11	7	Inf. Colic	
Bernstein & Kasich, 1974	2	20	21	10	Dyspepsia	
Bernstein & Schwartz, 1974	2	101	83	7	Dyspepsia	
Danhof, 1974	2	25	25	4	Post-Op.	
Eveld, 1977	2	40	40	10	IBS-like	Combination
Avramovic, 1979	2	50	50	2	Post-Op.	
Danielsson, 1985	2	27	27	7	Inf. Colic	Cross-over
Ogilvie, 1986	2	38	38	56	GOR	
Sethi, 1988	2	13	13	variable	Inf. Colic	Letter
Smart, 1990	1B	28	25	56	GOR	Combination
Grossi, 1993	2	10	10	56	GOR	CIS vs. Simeth+MCP*
Metcalf, 1994	1B	83	83	3–10	Inf. Colic	DBCO
Voepel-Lewis, 1998	1B	17	19	1	Post-Op.	pediatric
Wiberg JMM, 1999	2	25	25	14	Inf. Colic	Vs. spinal manipulation
Holtmann, 1999	1A	87	86	28	Dyspepsia	vs. Cisapride
Kaplan, 1999	1A	247	246	2	Diarrhoea	Monother. & Combin
Holtmann, 2002	1A	58	120	56	Dyspepsia	vs. Placebo & Cisapride
Chen, 2005	2	65	63	variable	Obstruction§	Combination
Savino, 2006	1B	103	96	14	Inf. Colic	hydrolysed formula
Hanauer, 2007	1A	244	239	2	Diarrhoea	Monother. & Combin
Savino, 2007	1B	42	41	28	Inf. Colic	Probiotic
TOTAL	2131	1912	1–56			

*) MCP = metoclopramide
§) Partial adhesive small-bowel obstruction
**) Quality ratings: 1A) All double-blind randomized controlled trials (RCTs) complying with GCP standards;
1B) All double-blind randomized controlled trials (RCTs) with adequate statistical reporting (intention-to-treat analysis) or raw data allowing for such an analysis;
2) All randomized controlled comparisons or equivalent, with statistical reporting;
3) For safety analysis only, all studies (including open) with complete reporting of safety.

with functional dyspepsia. One hundred and eighty-five patients with functional dyspepsia were randomized and treated in a double-dummy technique with simethicone (105 mg t.d.s.), cisapride (10 mg t.d.s.) or placebo (t.d.s.). The primary outcome measure was the O'BRIEN [36] global measure of the patients' rating of 10 upper gastrointestinal symptoms. Outcome measures were assessed at baseline and after 2, 4 and 8 weeks of treatment (intention-to-treat). After 2, 4 and 8 weeks, treatment with simethicone and cisapride yielded significantly (all P values <0.0001) better improvement of all symptoms as compared to placebo. Simethicone was significantly better than cisapride after 2 weeks (P=0.0007), but the differences were no

longer statistically significant after 4 and 8 weeks. Patients treated with simethicone judged the efficacy of their treatment as very good in 46% of cases, compared to 15% and 16% of the patients receiving cisapride and placebo, respectively (all P values <0.0001).

Irritable bowel syndrome (IBS)-like symptoms

The abdominal pain associated with irritable bowel syndrome may frequently be confused with the pain of functional dyspepsia, but it is generally associated with abnormal bowel habits. Since the trials conducted with simethicone did not apply validated criteria (e.g. Rome II criteria [37]), the term "IBS-like" symptom is employed in this paper.

Simethicone has been recommended for the management of bloating in irritable bowel syndrome, among a panoply of other possible therapies for the disorder [38], but there are no adequate prospective comparative studies. There are only 2 trials including 80 patients treated with simethicone and 54 control patients in the included database: 1.) OSWALD [39] reported in 1961 a placebo-controlled study with 50 mg simethicone tablets which favoured the active treatment, and 2.) in 1974, WEISS [40] published a review combined with an open study on 30 patients treated with simethicone, reporting favourable outcomes too. One placebo-controlled study using a combination of simethicone with other drugs in IBS-like symptoms is discussed below.

Simethicone in acute diarrhoea

Acute diarrhoea with gas-related abdominal discomfort is a common, usually self-limited disorder with substantial social and economic impact. Incidence rates of 0.53 to 0.55 per person-year have been reported for adults aged 20 to 39 years. There are multiple causes of acute diarrhoea, but in most cases the cause is thought to be infections, including those caused by viruses, bacteria, or parasites. Many patients with acute diarrhoea, regardless of cause, also experience gas, cramps, abdominal pain, bloating, distension, flatulence, nausea and vomiting.

KAPLAN et al. [41] compared the efficacy and safety of a loperamide hydrochloride-simethicone combination product with those of loperamide alone, simethicone alone, and placebo in treating acute diarrhoea with gas-related abdominal discomfort in a double-blind trial of 48 hours duration. A total of 493 adult outpatients participated who experienced acute non-specific diarrhoea with at least moderately severe abdominal discomfort. Each patient was randomly assigned to receive 2 chewable tablets containing 2 mg loperamide hydrochloride and 125 mg simethicone (n=124); 2 mg loperamide hydrochloride (n=123); 125 mg simethicone (n=123); or placebo (n=123). This was followed by 1 tablet after each unformed stool, up to 4 tablets in any 24-hour period. Time to last unformed stool and time to complete relief of gas-related abdominal discomfort were the protocol-specified primary outcomes. Patients who received loperamide-simethicone had a significantly ($P<0.001$) shorter time to last unformed stool and faster relief of gas-related abdominal discomfort than patients who received loperamide, simethicone, or placebo alone. Simethicone given alone was significantly ($P<0.01$) more effective than placebo for 'overall illness relief', 'diarrhoea relief', 'abdominal discomfort relief' and mean number of unformed stools in the period 36–48 hours (see Figure 3).

HANAUER et al. [42] recently reported a similar multicentre, double-blind, 48-h study in which patients were randomly assigned to receive two tablets,

Fig. 2. Functional dyspepsia: Difference between Simethicone & Reference in percent patients rating the result as 'very good' (Holtmann) or 'improved' (Bernstein & Kasich).

each containing either 2 mg loperamide hydrochloride and 125 mg simethicone (n=121), 2 mg loperamide hydrochloride (n=120), 125 mg simethicone (n=123), or placebo (n=121). Confirming the study by KAPLAN et al. [41], the median time to last unformed stool for the combination (7.6 h) was significantly shorter than that of loperamide hydrochloride (11.5 h), simethicone (26.0 h), and that of placebo (29.4 h) ($P<0.0232$; survival curves). With the combination the time to complete relief of gas-related abdominal discomfort was also shorter than among patients who received either active substance alone or placebo (all $p=0.0001$).

Post-operative management

The pathogenesis of postoperative ileus is complex, with multiple factors contributing either simultaneously or at various times during the development of this entity [43]. Although it is mentioned in training courses for medical students, it is difficult to assess the role of simethicone in the management of the post-operative patient. There are 4 trials including 847 patients treated with simethicone and 631 control patients in the included data-base. However, there are only fairly old trials in adult post-operative patients available. In one trial published in 1974

[44] the authors included 50 women undergoing caesarean section delivery or other elective pelvic surgery. Patients were randomly assigned to either simethicone 40 mg q.i.d. or placebo treatment, 4 times per day for 4 days beginning the first day after surgery. Most patients in both groups had gas pain and/or abdominal distension on the first and second days after surgery. However, on the second postoperative day, patients receiving simethicone had significantly more peristalsis and passage of flatus than those receiving the placebo. This earlier bowel activity was associated with earlier relief of symptoms. The differences were significant concerning spontaneous passage of flatus, audible bowel sounds, gas pain and need for heating pad. Favourable trends were seen at days 3 or 4 for abdominal distension, need for enema or rectal tube, but no effect on belching or spontaneous bowel movements. Similar results were reported by other authors in the 1970s in women undergoing caesarean section [45] or abdominal hysterectomy [46].

Simethicone may be an effective treatment choice for suspected postoperative abdominal discomfort in infants following administration of inhalational anaesthesia for minor surgery. In one, relatively small, double-blinded study [47], children were assessed for

Abb. 3. Relief of overall illness, diarrhoea and of abdominal discomfort. (Kaplan et al., 1999).

the presence of postoperative abdominal discomfort and, if evident, were randomly given either simethicone or placebo. Abdominal discomfort was measured using the Faces Legs Activity Cry and Consolability (FLACC) Behavioural Pain Scale. Scores were recorded during 30 minutes following drug administration and at discharge. Infants were given either placebo (n=19) or simethicone (n=17). Infants who received simethicone were comfortable earlier (FLACC Behavioural Pain Scale significantly lower after 20 and 30 min) and required fewer rescue medications compared with placebo (2 out of 17 vs. 9 out of 19; $P<0.05$). There were no differences in vomiting (simethicone 5 out of 17 vs. placebo 2 out of 19), ability to tolerate oral fluids prior to discharge (15 out of 17 vs. 19 of 19 respectively) or in the length of stay in the post-anaesthetic care unit (67 ± 20 vs. 68 ± 23 minutes respectively).

Paediatrics: infantile colics

For research purposes, WESSEL'S [48] 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. Systematic reviews of

the published literature (LUCASSEN [49], WADE [50]) found that the evidence concerning simethicone did not reach the threshold of significance in the 3 relatively small published placebo-controlled trials available [51,52,53]. Furthermore, the therapeutic effect of simethicone was compared in the 1970s with that of methylscopolamine in a single-blind crossover study [54], in 24 infants. The number of crying fits decreased significantly during the treatment periods with simethicone emulsion, while no changes were observed during the treatment with methyl scopolamine. However, two modern comparative trials found that Simethicone + standard milk formula was less effective than partially hydrolysed milk formula [55] (formula-fed infants, aged less than 4 months, 96 treated with the hydrolysed milk formula and 103 treated with 6 mg/kg simethicone twice daily) or a probiotic [56] (breastfed colicky infants, 41 treated with the probiotic and 42 with 60 mg daily simethicone).

Simethicone in combinations

The interest of these studies is limited since they do not provide information about the contribution of simethicone to any effect observed.

In one open comparative trial [57], oral therapy with magnesium oxide,

Lactobacillus acidophilus and simethicone (n=65) was effective in hastening the resolution of conservatively treated partial adhesive small-bowel obstruction and shortening the hospital stay in comparison to the "nothing by mouth"-group (n=63; both received intravenous hydration, nasogastric-tube decompression). These authors [58] have recently confirmed their findings on a larger group of patients (verum n=120 vs. controls n=116).

There were also numerous studies using combinations of drugs + simethicone in symptoms of gastroesophageal reflux. However, only three were controlled studies (comparing with an active reference) which included 76 patients treated with simethicone and 73 control patients. In one double-blind trial [59], the effect of the addition of dimethicone to an antacid gel in the treatment of reflux oesophagitis was assessed in 45 adult patients. The authors concluded that "both appear to be equally effective in ameliorating symptoms but dimethicone appears to confer a small but definite advantage in the healing of oesophagitis." Similar results were reported for dimethicone/antacid vs. alginate/antacid in another randomized trial [60]. In one small double-blind study [61] cisapride effervescent granules were reported to be more effective than a metoclopramide-dimethicone combination (no details on composition) in the treatment of gastroesophageal reflux disease.

There were numerous studies using combinations of drugs in IBS-like symptoms, only one old study, however, was placebo controlled [62] (simethicone 100 mg, papaverine 25 mg, enzymes derived from *Aspergillus oryzae* 120 mg); therapeutic success was reported in 31 out of 39 patients treated with verum, vs. 15 out of 40 placebo-treated patients.

Overview of clinical safety

The nature of the patient population and the extent of exposure, both for test drug and control treatments were equivalent and representative for the target populations. Approximately 2000 adults and 200 infants have received simethicone as a monotherapy in the examined database in studies reporting on safety. The majority of the

adult patients were between 40 and 64 years of age, with a predominance of female patients (2 out of 3) as could be expected from indications studied. Comparing the data concerning side effects/adverse events, serious adverse events and withdrawals due to side effects/adverse events, simethicone compared favourably with placebo, Cisapride, Loperamide and Loperamide + simethicone. No causal relationship has been established so far for any side effects/adverse events. No systematic laboratory findings nor cases of laboratory abnormalities in relation with simethicone have been reported in the literature.

The potential for overdosing also appears very small; healthy volunteers have ingested up to 30 g per day of simethicone during several days without adverse effects or biochemical abnormalities [5].

Discussion

Simethicone as an adjunct for the improvement of visibility in endoscopic examinations has a long history, since HIRSCHOWITZ et al. [63] compared several preparations in 1954. These uses are well established and have not been discussed here in detail.

Is there a need for an alternative therapy for functional dyspepsia? A recent systematic review [64] of the evidence concluded that histamin₂-receptor antagonists (H₂RA) and proton pump inhibitors (PPI) obtained a significant relative risk reduction compared to placebo (Grade of evidence: A). The same group concluded that *Helicobacter pylori* eradication therapy has a small but statistically significant effect in *H. pylori* positive patients (Grade of evidence: A) while they concluded that “there are very limited data to support the use of simethicone” (Grade of evidence: B). Bismuth salts, antacids and sucralfate are of limited or no interest and prokinetics, although some are probably effective, have fallen into some disrepute due to serious side effects. Simethicone was shown to be more effective than placebo in two trials and also to be more effective than cisapride – the best doc-

umented prokinetic – in two trials. In our view, the information provided by these studies and the favourable safety profile of simethicone seem to justify its use in functional dyspepsia as a first-line medication, particularly when bloating is a prominent feature.

Some old trials conducted with simethicone as a monotherapy support the use of this compound in the treatment of IBS-like symptoms. However, prospective randomized studies in this condition are needed.

In traveller's diarrhoea, the combination of simethicone with a μ -opioid-agonist provided faster and more complete relief, particularly of associated gas-related abdominal discomfort, than either of its components or placebo. The data also demonstrate the efficacy of simethicone alone compared with placebo in the treatment of abdominal discomfort associated with diarrhoea. The two studies available in traveller's diarrhoea are fairly large and well-conducted, confirmatory studies are desirable to generalize these results to the population with diarrhoea at large.

In the prevention of post-operative ileus, modern procedures and agents have reduced the risk [65]; most of these were not available or current practice at the time the studies with simethicone were conducted. Whether simethicone has a place among the current post-operative management of patients should be examined in studies ‘ad hoc’ employing modern procedures.

Infant colic continues to be a poorly understood problem for babies, parents, and physicians. Although some authors recommend simethicone as part of a stepwise management approach of infantile colics [66] or of Recurrent Abdominal Pain syndrome in children [], prospective studies have been inconclusive. However, ‘absence of evidence is no evidence of absence’.

Although the use of simethicone in fixed combinations ‘a priori’ seems a sensible approach if the individual components have been shown to be effective, the evidence concerning the use of such combinations in symptomatic relief of GOR or IBS must be regarded as clearly insufficient and not up-to-date.

Conclusion

Simethicone may well turn out to be a gastroenterological ‘Cinderella’*. After all, it seems a valuable alternative in the various indications in which its intraluminal defoaming and coating action may be beneficial. Several modern and well-conducted RCTs have shown that this may be the case in traveller's diarrhoea or in functional dyspepsia, in addition to its well-established uses in diagnostic procedures. More RCTs will be needed, particularly in IBS, post-surgical patients and paediatrics, if we want to know the end of the story. One advantage seems to be playing in favour of simethicone all along: its very large safety margin.

* Cinderella; or The Little Glass Slipper (France, Charles Perrault), also known as The Cinder Maid or Aschenputtel (Germany, Jacob and Wilhelm Grimm, version of 1812)

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