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Helicobacter pylori in Patients with Systemic Sclerosis: Detection with the ^{13}C-urea Breath Test and Eradication

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In patients with systemic sclerosis peristaltic abnormalities may delay gastric emptying, giving rise to bacterial overgrowth, including possibly *Helicobacter pylori* (HP). Infection with *Helicobacter* is an important risk factor for esophageal and gastric diseases, including esophagitis, gastritis and gastric cancer.
The purpose of this prospective study was to assess gastric HP infection in patients with systemic sclerosis. In 12 patients with systemic sclerosis the newly introduced breath test with ^{13}C-labelled urea was used for indirect detection of gastric urease activity due to HP infection. Five out of 12 patients gave *Helicobacter*-positive results (42%); 7 patients were negative for *Helicobacter* colonization (58%). Thus, the risk for gastric diseases caused by HP infection is enhanced in patients with systemic sclerosis compared with white healthy, asymptomatic persons examined in other studies.
Helicobacter-positive patients were treated with 2 × 20 mg omeprazole and 4 × 500 mg amoxicillin over 14 days. Afterwards the ^{13}C-urea breath test was repeated and showed negative results for *Helicobacter* in all systemic sclerosis patients treated. Dual therapy with omeprazole and amoxicillin therapy effectively eradicated HP. The ^{13}C-urea breath test did not cause any side-effects and is therefore considered to be a non-invasive, non-toxic and safe method for the diagnosis and therapeutic control of *Helicobacter*-status. *Key words: stable isotope; omeprazole; amoxicillin.*

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Gastrointestinal disease is one of the most commonly recognized visceral manifestations of systemic sclerosis (SSc) (1–3). Dysphagia and reflux esophagitis are believed to be caused by esophageal dysmotility and reflux that can lead to peptic esophagitis, Barrett's metaplasia, esophageal strictures and cancer. Hypomotility is not restricted to the esophagus but may also be present in the lower part of the gastrointestinal tract. Peristaltic abnormalities delay gastric emptying, giving rise to bacterial overgrowth with consecutive pseudoobstruction or malabsorption (3). Little is known about bacterial overgrowth, e.g. *Helicobacter pylori* (HP), of the upper gastrointestinal tract in patients with SSc. Since the detection of HP in 1983 (4), interest has focused on its prevalence in various gastrointestinal diseases. Infection with HP is now generally accepted as a major pathogenetic factor in esophageal diseases, gastritis, peptic ulceration, gastric lymphomas (MALT), abdominal lymphadenopathy and gastric cancer (5–7).

Although an increased susceptibility for infection with HP can be expected in patients with SSc suffering from esophageal or gastric hypomotility and abdominal pain, this could not be confirmed until now. The present study examined whether infections with HP are more frequent in SSc patients with gastrointestinal involvement. In addition, the efficacy of a treatment regimen using omeprazole and amoxicillin (8) for eradication of HP was examined.

The non-invasive ^{13}C-urea breath test was used for detecting the possible presence of HP in SSc patients with reflux esophagitis and dyspepsia (9).

PATIENTS AND METHODS

Patients

Twelve patients (9 females, 3 males, mean age 56 years, range 36–77 years) suffering from SSc according to the criteria of the "Arbeitsgruppe Sklerodermie der Arbeitsgemeinschaft Dermatologische Forschung" (10) and LeRoy et al. (11) were entered into the study. One patient was classified as type I (acrosclerosis distal to the wrist; international classification: limited disease), 11 as type II (sclerosis proximal to the wrist; international classification: rapid cutaneous sclerotic progression). There was no patient classified as type III (diffuse sclerosis) (Table I). The diagnosis of SSc was based on clinical criteria, dermatohistopathology and increased titres of antinuclear antibodies (Hep-2 cell test) or Anti-Scl-70 antibodies. Esophageal involvement was assessed by scintigraphic imaging. All patients had ?????? complaints with dysphagia, reflux esophagitis and gastrospasm, but only patients 4, 5, 7, 9, 10, 11, and 12 (Table I) had dyspepsia, postprandial epigastric pressure or mid-epigastric pain (Table II). These symptoms of the upper gastrointestinal tract can be related to HP infection. Three patients took omeprazole 20 mg per day for reflux esophagitis.

Methods

On biochemical characterization, HP proved to have a powerful urease activity and this property has been exploited in attempts to simplify the diagnosis of HP infection. The urease activity of HP can be distinguished from that of colonic bacteria by the rapidity and extent of

Table I. *SSc patients investigated by the ^{13}C-urea breath test*

SSc type according to 10 and 11 (ld: limited disease, rcsp: rapid cutaneous sclerotic progression).

Pat. No.	Age/ Sex	SSc-type (10/11)	Esophageal involvement	HP-status before treatment	HP-status after treatment
1	45/F	I/ld	+	○	○
2	77/F	II/rcsp	+	○	○
3	70/F	II/rcsp	+	○	○
4	52/F	II/rcsp	+	+	○
5	58/F	II/rcsp	+	○	○
6	53/F	II/rcsp	+	○	○
7	46/M	II/rcsp	+	+	○
8	70/F	II/rcsp	+	○	○
9	59/F	II/rcsp	+	+	○
10	55/M	II/rcsp	+	+	○
11	36/M	II/rcsp	+	+	○
12	58/F	II/rcsp	+	○	○

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Table II. *Upper gastrointestinal complaints before and after eradication of HP*

Gastrointestinal complaints before therapy	Relieved after HP-eradication
Dysphagia	No
Reflux esophagitis	Yes
Dyspepsia	Yes
Postprandial epigastric pressure	Yes
Mid-epigastric pain	Yes
Gastrospasm	Yes

urea hydrolysis in HP-infected individuals (12). An excellent correlation between the results of the breath test, the bacterial culture and the histological evaluation as well as a high specificity, sensitivity and validity of the breath test have been proved (13–15). Therefore, the ^{13}C-labelled urea breath test is considered to be the gold standard in the detection of HP.

Briefly, after the patients had been fasting for at least 6 h, 150 ml 0.1 N citric acid (Merck, Darmstadt, Germany) was administered to inhibit gastric emptying. One minute later all patients received 20 ml 0.1 N citric acid containing 75 mg ^{13}C-urea (99% ^{13}C, Cambridge Isotope Laboratories, Woburn, U.S.A.) followed by 30 ml citric acid. Breath samples (1500 cm^3) were collected before and 1, 10, 20, 30, 45, 60 and 90 min after ingestion of the tracer (12, 13).

The $^{13}CO_2/^{12}CO_2$-ratio (δ-value) of the expired breath was measured using CEDIOX™ breath test (Eppendorf, Hamburg, Germany) (9). All results of the ^{13}C-urea breath test were calculated as recovery of $^{13}CO_2$ in the expired breath as δN:

$$\delta N = \delta \times \frac{\text{body weight}}{\text{tracer dose}} \text{ [kg/mMol]}$$

Special attention was paid to the accuracy of this technique, because the measurement is not under control of a reference standard. Usually, ^{13}C-isotope abundance (^{13}C‰) is expressed as the promille relative difference from the reference standard, Pee Dee Belemnite (PDB) Limestone (South Carolina, U.S.A.) (15). The percentage of ^{13}C in the PDB standard is higher than in organic carbon of the biosphere. Hence, the ^{13}C-values of organic carbon have a negative value on the PDB scale. Therefore, the accuracy and precision of this method were proved by using isotope ratio mass spectrometry (IRMS) (Finnigan MAT, Bremen, Germany). The results of CEDIOX™ showed a good correlation to the PDB standard. The CEDIOX™ was used for the measurements of this study, because the collection of exhaled breath by using a sampling cartridge is easier than by vacutainer for IRMS. Moreover, this system avoids liquid nitrogen, bulky storage and dangerous handling. The δN-values for a HP-negative status corresponded to $^{13}CO_2$ abundance without ingestion of the ^{13}C-labelled tracer. A HP-positive status was considered as a δN-value 5–6-fold higher than the basal value. In HP-positive patients the ^{13}C-urea breath test was repeated; the time interval between finishing the treatment and re-examination was 4 weeks. Side-effects after ingestion of the tracer ^{13}C-urea or citric acid were not observed in any of the patients.

HP-positive patients were treated with the proton-pump inhibitor omeprazole 2 × 20 mg daily in combination with the antibiotic suspension amoxicillin 4 × 500 mg per day preprandially for 2 weeks. After this therapeutic regimen, omeprazole treatment was continued at 20 mg/day for 4 weeks. There was no history of simultaneous treatment with bismuth salts or other antibiotics, pregnancy, known omeprazole or amoxicillin allergy, stomach resection or putative lack of compliance.

RESULTS

All patients tolerated the ingestion of citric acid and of the tracer ^{13}C-urea well. The test did not cause gastric discomfort or other side-effects.

Five out of 12 patients with SSc gave HP-positive results (42%) (Fig. 1A); 7 patients were negative for HP infection (58%) (Fig. 1B). HP-positive SSc patients showed a rapid rise in $^{13}CO_2$ expiration within 30 min after ingestion of ^{13}C-urea. By contrast, the average δN-values of HP-negative patients corresponded to $^{13}CO_2$ abundance without ^{13}C-labelled tracer (blank sample). The repeated ^{13}C-urea breath test of the HP-positive patients treated with omeprazole/amoxicillin gave negative results for the increase of urease activity in all cases. Hence, this therapy showed an effective eradication of HP in all of the HP-positive SSc patients with relief of gastric complaints like reflux esophagitis, dyspepsia, postprandial epigastric pressure, mid-epigastric pain or gastrospasm. Dysphagia was not improved (Table II). Two patients experienced side-effects of the therapy: self-limiting diarrhea ($n = 1$) and nausea ($n = 1$). Lower detection of exhaled $^{13}CO_2$ was observed in the SSc patients taking omeprazole before entering the study than in other HP-positive patients.

DISCUSSION

Acute gastric infection with HP may produce symptoms such as abdominal pain, irritability, vomiting and malaise (4, 17). In some cases, the pain pattern may become chronic and has been associated with non-ulcer dyspepsia (17). Chronic HP infection plays a pathogenetic role in esophageal diseases, gastritis, peptic ulceration, MALT, abdominal lymphadenopathy and gastric cancer (5–7).

Many patients with SSc suffer from gastrointestinal involvement, including hypomotility of the esophagus and stomach, peptic esophagitis, dysphagia or reflux esophagitis (1–3, 10). Peristaltic abnormalities delay gastric emptying, giving rise to bacterial overgrowth (3), including possibly HP.

The standard methods available for the detection of HP infection are microbiological culture, histology and quick urease tests, which all depend on endoscopy and antral mucosal biopsies (14). The possibility of taking a positive biopsy sample in an HP-positive patient is restricted due to the known patchy distribution of HP in the stomach (13). The ^{13}C-urea breath test has become the best available diagnostic procedure to detect HP infections of the stomach because ^{13}C-urea in solution reaches

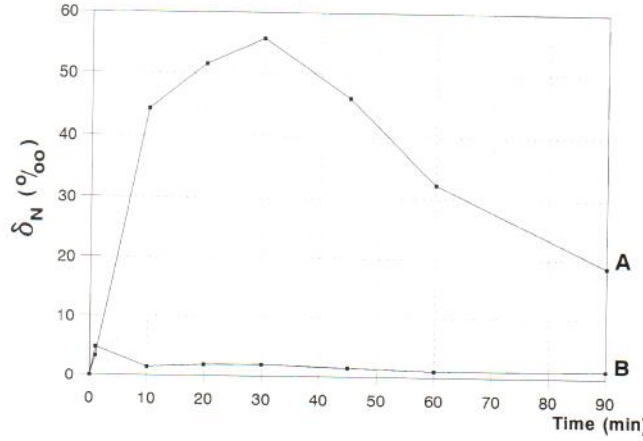

Fig. 1. $^{13}CO_2/^{12}CO_2$-ratio (δ_N-value) of ^{13}C-urea breath test giving positive (A) or negative (B) results for urease activity due to *Helicobacter pylori*.

every area of gastric mucosa. Moreover, the test shows high specificity and sensitivity, does not cause any side-effects and is non-invasive, non-toxic and safe (9, 12–14).

HP could be detected in 42% of the SSc patients using the ^{13}C-urea breath test. Biewer et al. found an enhanced frequency of HP infection (67,6%) in patients suffering from rheumatoid arthritis (18). Other collagenoses have not been studied yet. Compared with the 20–34% incidence of gastric HP in white healthy, asymptomatic persons (19, 20), we found an enhanced frequency of HP infection in patients with SSc. However, attention should be focused on this result because the incidence of HP colonization also depends on age, local sanitary conditions and geographic location (17, 19–21), and an age-matched control group was not examined. Although present reports suggest that bacterial colonization plays a relatively minor role in the pathogenesis of reflux esophagitis (20, 21), HP infection in SSc patients and patients with other collagenoses, like rheumatoid arthritis, may play an additional role in the clinical syndrome of gastrointestinal reflux as hypothesized by other authors (17, 18, 20). After HP had been eradicated, our HP positive SSc patients were relieved of their complaints, like reflux esophagitis, dyspepsia, postprandial epigastric pressure, mid-epigastric pain or gastrospasm. The improvement of reflux esophagitis may be attributed to the specific effect of omeprazole and is therefore not considered to be related to HP eradication. The esophageal and gastral hypomotility may be the underlying cause for the enhanced infection rate with HP in SSc patients.

Several reports suggest that HP might be eliminated under monotherapy with the H^+-K^+-ATPase inhibitor omeprazole (22). In contrast, all of the examined SSc patients taking omeprazole for reflux esophagitis ($n = 3$) were positive for HP. This group showed lower levels of exhaled $^{13}CO_2$ than other HP positive patients, probably caused by reduction of bacterial colonization in gastric mucosa. Thus, omeprazole monotherapy was found to be not suitable to eradicate HP in SSc patients, in agreement with Wagner et al., who examined 50 patients with upper gastrointestinal symptoms and chronic active gastritis (23).

The best eradication rates of HP have been reported with combination schedules using a bismuth salt, metronidazole, and amoxicillin or tetracycline (triple therapy) (12). The eradication rates for triple therapy were between 77 and 91%, depending on the duration of therapy (12, 24). However, triple therapy caused a high incidence of side-effects, endangering a sufficiently high compliance rate (8, 12, 24). The high cost of oral triple therapy is another reason to search for new modalities. In our study omeprazole was used in a dosage of 40 mg per day in combination with amoxicillin 4×500 mg per day for 2 weeks, showing high efficacy and minimal side-effects. In conclusion, combined omeprazole/amoxicillin therapy is a simple and effective approach for eradicating HP in patients with SSc.

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