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SUSCEPTIBILITY OF Helicobacter pylori FOR TOPICAL ANTIBIOTICS IN VITRO AND IN VIVO

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Chapter 8

Susceptibility of Neisseria meningitides for Tetracyclines

In Vitro and In Vivo
Abstract

Background: Resistance to systemically applied antibiotics is emerging in Helicobacter pylori infection. Topically applied antibiotics have not been studied extensively in the treatment of H. pylori infection. In a previous study we have shown that H. pylori was effectively suppressed by selective decontamination of the digestive tract (SDD) during intensive care stay. In the present study we determined the susceptibility of H. pylori to the topically applied antibiotics used in SDD in vitro and in vivo.

Methods: H. pylori infection was assessed by Laser-assisted-ratio-analyser (LARA)-$^{13}$C-urea breath test and detection of H. pylori antibodies in patients' serum. The in vivo susceptibility of H. pylori to the SDD antibiotics was assessed in two ways: 1) Ten critically ill H. pylori positive patients were treated with SDD, comprising intravenous cefotaxime and 3 topical antibiotics (polymyxin, tobramycin and amphotericin B) administered via a nasogastric tube. 2) Six H. pylori positive volunteers were treated with the topical antibiotics without intravenous cefotaxime to determine the effect of the topical antibiotics alone on H. pylori. The in vitro susceptibility to the SDD antibiotics and other antibiotics that are frequently used in the intensive care unit was studied for 11 H. pylori strains, obtained from critically ill patients.

Results: Conversion from a positive into a negative LARA-$^{13}$C-urea breath test within 7 days of SDD treatment occurred in nine of ten critically ill patients. In all 6 volunteers who were treated with the topical antibiotics alone, the LARA-$^{13}$C-urea breath test converted from positive to negative test after 7 days. Eight weeks after cessation of the topical antibiotics, 5 of the 6 volunteers re-converted from a negative to a positive LARA-$^{13}$C-urea breath test. The critically ill patients did not convert into a positive test as long as the SDD treatment was continued. The in vitro studies revealed that all strains were susceptible for cefotaxime and tobramycin, indicating that both antibiotics caused the suppression of H. pylori in the critically ill patients but tobramycin alone in volunteers. The strains were not susceptible for polymyxin or amphotericin B.

Conclusion: H. pylori was effectively suppressed by the SDD regimen, containing both intravenous cefotaxime and topical tobramycin. Topical tobramycin alone could suppress H. pylori in all cases but a recrudescence occurred frequently after cessation of treatment.
Introduction

_Helicobacter pylori_ plays a pivotal role in the development of virtually all duodenal ulcers and many gastric ulcers [1]. Eradication of _H. pylori_ prevents recurrence of duodenal and gastric ulcers and is therefore indicated in patients with ulcer disease [2]. _H. pylori_ is also associated with gastric carcinoma and gastric lymphoma [3]. It has been hypothesised that _H. pylori_ is a risk factor for stress ulceration in the critically ill patient [4]. We have also shown that patients treated with selective decontamination of the digestive tract (SDD) appear to have a lower incidence of stress ulcer related bleeding [5], which may at least in part be related to suppression of _H. pylori_ infection. SDD is used to prevent infections in critically ill patients and was recently shown to reduce mortality by 20% [6]. In a previous study we found that _H. pylori_ was effectively suppressed in critically ill patients who were treated with SDD but these patients were also treated with various other antibiotics [7]. Critically ill patients in the intensive care unit are frequently treated with multiple systemic and topical antibiotics. The full SDD protocol contains both topical antibiotics (polymyxin, tobramycin and amphotericin B) and systemic cefotaxime [8]. However, topical antibiotics have not been tested extensively in the treatment of _H. pylori_. Currently, triple therapy with a protonpump inhibitor and two systemically acting antibiotics is the treatment of choice for the eradication of _H. pylori_ with eradication rates around 90% [9]. Most triple therapies include two of the antimicrobial agents amoxicillin, metronidazole or clarithromycin but resistance to these antibiotics is emerging [10,11]. Therefore new antibiotic treatment strategies may be needed in the future. The antibiotics used nowadays to eradicate _H. pylori_ act mainly systemically after absorption from the digestive tract and subsequent active or passive excretion in the gastric mucosa [12]. It is unknown whether the topical, non-absorbable antibiotics which are used in SDD are able to suppress or eradicate _H. pylori_. In the present study we determine whether _H. pylori_ is suppressed after administration of the full SDD regimen, containing both the topical and the systemic SDD antibiotics, while no other antibiotics are given. In addition, to determine the role of topical SDD antibiotics _H. pylori_ positive volunteers are treated with the topical SDD components alone. _In vitro_ studies are performed to determine the susceptibility of _H. pylori_ for these SDD antibiotics and other antibiotics frequently used in the intensive care.
Methods

Patients
Patients were included when admitted to the intensive care unit for emergency reasons and when mechanically ventilated. Informed consent was obtained from the nearest relatives. On admission both urea breath test and serology were performed to detect *H. pylori* infection. All patients were treated with SDD which consisted of 3 parts: 1) a mixture of the non absorbable PTA antibiotics (Polymyxin E 100 mg, Tobramycin 80 mg and Amphotericin B 500 mg) which was given by nasogastric tube four times daily during the entire intensive care stay, 2) a 2% solution of PTA in orabase paste which was administered topically to the oropharynx four times daily during the entire intensive care stay and 3) cefotaxime 1000 mg four times daily intravenously during the first four days of admission. Patients were excluded when other antibiotics were used during the study period. The study was approved by the local ethical and scientific committees.

Volunteers
Healthy volunteers positive for *H. pylori* as detected by LARA-\(^{13}\)C-urea breath test and serology were included. They were treated with the topical antibiotics that were used in SDD (polymyxin E 100 mg, tobramycin 80 mg and amphotericin B 500 mg). These antibiotics were taken orally four times daily during food intake for 7 days. The volunteers did not use other medication.

Detection of *H. pylori*

Urea breath test
The Laser Assisted Ratio Analyser (LARA)-\(^{13}\)C-urea breath test (Alimenterics, Morris Plains, New Jersey, USA) has been validated for mechanically ventilated intensive care patients [13]. In the current study a LARA-\(^{13}\)C-urea breath test was performed immediately after admission to the intensive care unit and institution of mechanical ventilation. Repeated urea breath tests were done in the patients on the third and seventh day and every seventh day thereafter until discharge from the intensive care unit. No follow up was applied after discharge of the intensive care unit. The volunteers performed a LARA-\(^{13}\)C-urea breath before treatment and repeated a such a breath test one day and 8 weeks after cessation of treatment. Previously, we have shown the LARA-\(^{13}\)C-urea breath test to be an easy and reliable method to detect *H. pylori* and eradication after treatment. Sensitivity and specificity were 95% and 94% respectively in ambulant patients with a positive predictive value of 95% and a negative predictive value of 94% [14]. In mechanically ventilated intensive care patients sensitivity was 94%, spe-
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cificity 92%, positive predictive value 88% and a negative predictive value 96% [13].

Serology
IgG antibodies against H. pylori were detected by enzyme linked immuno-
sorbent assay (HM-CAP™ ELISA Enteric Products, Inc. Stony Brook, NY). A cut off level of 1.8 U/l was used. When compared to urea breath test in ambulant patients sensitivity of this test was 98.7%, specificity and positive predicting value were both 100% and negative predicting value was 98.6% [15]. Sera were drawn immediately after intensive care admission and on the third and the seventh day and every 7th day thereafter.

Definition of H. pylori infection:
H. pylori infection was diagnosed when both the Laser Assisted Ratio Analyser (LARA)-13C-urea breath test and serology were positive on admission.

Culture and Minimal Inhibitory Concentrations
Upper gastrointestinal endoscopy was performed in the patients with normal haemostatic parameters and within 6 hours after intensive care admission before any antibiotic treatment was given. Two biopsies were taken from the antrum and two from the corpus. Biopsies were stored in phosphate buffered saline and kept in a refrigerator until bacteriological culturing within 12 hours. Cultures were prepared by rubbing biopsy specimens on the surface of horse blood agar plates (5% defibrinated horse blood Columbia agar base, Oxoid CM 331, Unipath, Basingstoke, England) and horse blood agar plates containing Dent supplement (Unipath). The culture plates media were incubated at 35°C for 10 days in a microaerophylic atmosphere (5% O2, 10% CO2 and 85% N2). H. pylori were identified on the basis of typical colony morphology, characteristic appearance on Gram staining, and positive urease, oxidase, and catalase. The susceptibility to tobramycin, cefotaxime, amoxicillin, ciprofloxacin, vancomycin, metronidazole and amphotericin B was assessed by E-test (AB Biodisk, Solna, Sweden) on horseblood agar plates in a microaerophylic atmosphere according to the instructions of the manufacturer. Susceptibility to polymyxin E was assessed by agar diffusion on horseblood agar using tablets containing 150 microgram polymyxin (Neo-Sensitabs, Rosco, Denmark).
Results

Ten intensive care patients were included in the study and treated with SDD, containing both topical antibiotics and intravenous cefotaxime. Nine patients converted from a positive into a negative LARA-\textsuperscript{13}C-urea breath test within 7 days of treatment (7 within 3 days; 2 within 7 days). The other patient did not convert into a negative test after 7 days of treatment and was discharged from the intensive care on the 8\textsuperscript{th} day. In the patients with a conversion into a negative test, repeated urea breath tests were negative as long as the topical antibiotics were given (range 3.5 to 33 days, mean 10.8 days). One patient was readmitted 4 months later and had a repeated urea breath test which was negative, indicating eradication of the organism. Three patients died in hospital. The other 6 patients did not have repeated tests after the antibiotics were discontinued and after discharge from the intensive care unit.

The 6 volunteers receiving topical SDD antibiotics without cefotaxime converted to a negative urea breath test within 7 days of treatment. However, 5 of them had a positive LARA-\textsuperscript{13}C-urea breath test 8 weeks after cessation of the antibiotic treatment. Therefore, topical antibiotics effectively suppress \textit{H. pylori} infection. However, overt eradication occurred in only one of 6 volunteers.

Eleven strains of \textit{H. pylori} obtained from 7 critically ill patients were cultured and susceptibility to the antibiotics used in SDD treatment as well as for other commonly used antibiotics on our intensive care unit was determined (table 1). Metronidazole resistance was found in only one \textit{H. pylori} isolate. Resistance to polymyxin E was present in 4 strains that were tested for polymyxin E resistance. All 11 \textit{H. pylori} isolates were susceptible to cefotaxime and tobramycin, mean MIC of 0.002 and 0.85 mg/l respectively. This result indicates that the latter two antibiotics contributed to the suppression of \textit{H. pylori}, whereas the other SDD components did not.
Table 1
Minimal inhibitory concentrations (mg/l) as determined by E-test of 11 Helicobacter pylori strains from critically ill patients for antibiotics that are frequently used in the intensive care unit and in SDD. R; resistant. ND; not determined.

<table>
<thead>
<tr>
<th>Strain:</th>
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<tbody>
<tr>
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<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
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<td>0.75</td>
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<td>1.0</td>
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<td>0.016</td>
<td>0.19</td>
<td>0.094</td>
<td>0.19</td>
<td>0.064</td>
<td>0.032</td>
<td>0.032</td>
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<tr>
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<td>&lt;0.016</td>
<td>&lt;0.016</td>
<td>0.016</td>
<td>0.016</td>
<td>0.032</td>
<td>&lt;0.016</td>
<td>&lt;0.016</td>
<td>&lt;0.016</td>
<td>0.032</td>
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<tr>
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<td>0.032</td>
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<td>0.38</td>
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<td>0.38</td>
<td>0.064</td>
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<td>&gt;256</td>
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<td>Metronidazole</td>
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<td>0.38</td>
<td>0.75</td>
<td>&gt;256</td>
<td>1.0</td>
<td>0.75</td>
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<tr>
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<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>ND</td>
</tr>
<tr>
<td>Polymyxin</td>
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<td>R</td>
<td>R</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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Discussion

In a previous study we have shown that H. pylori was effectively suppressed in critically ill patients who were treated with various antibiotics in addition to the SDD antibiotics [7]. However, it was not clear whether H. pylori suppression would be effective when only the SDD antibiotics were used and if so, whether the suppression was due to either the topical or the systemic antibiotics used in SDD. Therefore, in this study we treated patients with the entire SDD regimen (topical and systemic) whereas H. pylori positive volunteers were treated with the topical SDD antibiotics alone. The present study showed that H. pylori was effectively suppressed in all but one of the patients who were treated with the full SDD regimen, consisting of both the topically administered antibiotics (Polymyxin, Tobramycin and Amphotericin B (PTA)) and the intravenously administered cefotaxime. Treatment with the topical PTA antibiotics alone also resulted in suppression of H. pylori infection. However, cessation of the topical treatment with the PTA antibiotics after 7 days resulted in reappearance of H. pylori in all but one person. Determination of eradication rate in the patients treated with both the PTA antibiotics and intravenous cefotaxime was not possible because follow up after intensive care discharge was impossible to obtain. In critically ill patients the H. pylori eradication rate might have been higher than in vol-
unteers because the critically ill patients received additional cefotaxime and the topical PTA antibiotics were given longer compared to the volunteers. Longterm follow up was obtained in only one intensive care patient and revealed successful *H. pylori* eradication. This patient was treated with intravenous cefotaxime during 4 days and the topical PTA antibiotics during the 5 weeks that the patient was admitted at the intensive care unit.

To determine which of the SDD antibiotics contributed to *H. pylori* suppression *in vitro* susceptibility tests were performed. The *in vitro* susceptibility tests (table 1) showed that cefotaxime and tobramycin were the two agents from the SDD regimen that exerted anti-*H. pylori* properties. Since the topical PTA antibiotics does not comprise cefotaxime and *H. pylori* was unsusceptible for polymyxin and amphotericin B, tobramycin exclusively served as a monotherapy against *H. pylori*. Some antibiotics might be efficacious against *H. pylori* when administered as a monotherapy as was previously described using clarithromycin in a small percentage of patients (14 to 40%) who were treated for respiratory tract infections [16]. In the present study monotherapy with oral tobramycin resulted in a modest eradication rate (1 out of 6 persons). Monotherapy with oral tobramycin resulted in suppression of *H. pylori* in patients during their entire intensive care stay.

In general, topical treatment of *H. pylori* may have advantages above systemic treatment. Non-absorbable antibiotics lack systemic effects and may therefore lead to lesser side effects and greater patient compliance. Polymyxin E, tobramycin and amphotericin B are non-absorbable antibiotics effective in decontaminating the digestive tract from potentially pathogenic micro-organisms [8]. Gram positive flora is not affected by these antibiotics and therefore colonisation resistance remains intact. The wide use of these antibiotics in critically ill patients is not associated with emergence of antimicrobial resistance until now [17-19]. In a recent meta-analysis concerning SDD in critically ill patients in 33 studies with 5727 patients no resistance could be observed [6]. In some previous studies SDD was not associated with a significant mortality reduction [20-24]. However, the latest meta-analysis showed that properly used SDD resulted in a reduction of the incidence of ventilator associated pneumonia of 65% and a mortality reduction of 20% [6]. In a recent prospective study these results were confirmed [25]. In the present study a similar SDD regimen was used. It was shown previously that stress ulceration was virtually absent in a patient cohort which was treated with SDD, although other components of intensive care treatment may have contributed to the low incidence of stress ulcer related bleeding too [5]. In the present study we showed that *H. pylori* is effectively suppressed by the SDD antibiotics. The *in vitro* susceptibility tests indicate that polymyxin E and amphotericin B do not contribute to *H. pylori* suppression. In
contrast, the oral administration of non-absorbable tobramycin appears to be an active antimicrobial agent against *H. pylori*. Previously, we found that the presence of *H. pylori* infection in critically ill patients was a risk factor for the severity of gastric mucosal lesions [4]. The demonstrated suppression of *H. pylori* in critically ill patients treated with SDD might contribute to the prevention of stress ulcer formation in these patients.

In conclusion we have shown that selective decontamination of the digestive tract with the combination of intravenous cefotaxime and topical PTA antibiotics suppresses *H. pylori* effectively in critically ill patients. Also, the topical PTA antibiotics alone do suppress *H. pylori* but do not eradicate the infection frequently. *In vitro* studies indicate that cefotaxime and tobramycin are the two active components of SDD against *H. pylori*. Whether SDD results in reduction of stress ulcer formation by suppression of *H. pylori* is subject for future studies.
References


