Systemic antibiotic therapy in periodontics
Winkel, E.G.

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CHAPTER 6

ADDITIONAL CLINICAL AND MICROBIOLOGICAL EFFECTS
OF AMOXICILLIN AND METRONIDAZOLE AFTER INITIAL
PERIODONTAL THERAPY

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Abstract

The aims of this study were to evaluate the clinical and microbiological effects of initial periodontal therapy (IT) and to determine the additional effects of systemic amoxicillin (Flemoxin Solutab®) 375 mg TID plus metronidazole 250 mg TID therapy, in patients with adult Actinobacillus actinomycetemcomitans (Aa) -associated periodontitis in conjunction with either Porphyromonas gingivalis (Pg), Bacteroides forsythus (Bf) and/or Prevotella intermedia (Pi). In addition the adverse effects of the antimicrobial therapy were also documented. A total of 22 patients were enrolled. The deepest, bleeding pocket in each quadrant was selected and at these 4 experimental sites clinical measurements and microbiological testing was carried out at baseline, after (IT), i.e., 21 weeks after baseline, and after antimicrobial therapy (AM), i.e., 35 weeks after baseline. At baseline the mean plaque index (PI) amounted 0.5, 0.1 after IT and 0.3 after systemic AM. The mean bleeding index decreased from 1.6 to 1.2 after IT and a further decrease to 0.7 after AM was noted. Suppuration was completely eliminated after AM. The mean change of probing pocket depth (PPD) after IT amounted 1.4 mm and was further reduced with an additional mean change of 1.1 mm after medication. Clinical attachment gain was 1.1 mm after IT and an additional 0.9 mm was observed after AM. One of the 22 Aa positive patients and 4 of 17 Pg positive patients became negative for these species after IT. The number of patients with detectable Pi decreased from 16 to 10 after IT. After AM, in comparison to baseline, suppression below detection level for Aa was achieved in 19 out of 22, for Pg in 9 out of 17, for Bf in 13 out of 14, and for Pi in 11 out of 16 patients. By contrast, higher frequencies of Peptostreptococcus micros and Fusobacterium nucleatum were found after AM. On the basis of the microbiological results the study group was separated into 2 subgroups: group A consisted of subjects who had no detectable levels of Aa, Pg, Bf and <5% of Pi after AM. Group B consisted of those who still showed presence of one of these 3 species and/or ≥5% levels of Pi. After AM, group B had significantly higher PI, BI, PPD and CAL scores than group A. It is concluded that group A showed low plaque scores and no detectable periodontal pathogens. This microbiological condition has been associated with a long-term stable periodontium.

Introduction

Periodontal disease may be thought of as a number of infections caused by bacteria that affect individual or multiple periodontal sites. One aim of periodontal therapy is to halt further loss of periodontal attachment. This is achieved by meticulous supra- and subgingival debridement that results in the reduction of the
total bacterial load. In addition, suitable supragingival plaque control measures are important to prevent recolonization of periodontal pathogens (Magnusson et al. 1984).


Wennström et al. (1987) showed that no clinically significant loss of attachment occurred during a 1-year observation period in the absence of *A. actinomyctemcomitans*, *P. gingivalis* and < 5% of *P. intermedia*. In contrast, in patients with one or more of these indicator bacteria, 20% of the sites exhibited clinical attachment loss of ≥ 2 mm within 1 year. In a 5-year follow-up study, Dahlén et al. (1996) investigated the association between the recurrence of periodontal pathogens and recurrent attachment loss. Reappearance of *A. actinomyctemcomitans*, *P. gingivalis* and *P. intermedia* was observed in 9 of 13 patients. In 6 of these 9 patients further periodontal attachment loss was observed. Patients without detectable subgingival *A. actinomyctemcomitans*, *P. gingivalis*, *P. intermedia* during the maintenance period of 5 years remained clinically stable.

Since it has been shown that *A. actinomyctemcomitans* is difficult to eliminate by mechanical means alone (Christersson et al. 1985, Goené et al. 1990, Kornman & Robertson 1985, Mombelli et al. 1994a, Renvert et al. 1990b,c), the practicality of antibiotics in the treatment of *A. actinomyctemcomitans*-associated periodontitis may be inferred. In this respect the use of amoxicillin plus metronidazole after completion of the initial periodontal therapy has been advocated (Van Winkelhoff et al. 1989, 1992). Yet, so far, the additional effects of amoxicillin plus metronidazole apart from the initial periodontal therapy have not been well documented.

The aims of the present investigation were to evaluate the clinical and microbiological effects of mechanical initial periodontal therapy and to determine the additional effects of amoxicillin plus metronidazole therapy in patients with adult *A. actinomyctemcomitans*-associated periodontitis, in conjunction with either *P. gingivalis*, *B. forsythus* and/or *P. intermedia*. Also in this study, the adverse effects of the antimicrobial therapy were documented.
Material and Methods

Patients

A total of 22 patients, comprising 7 males and 15 females, were enrolled in this study. The mean age was 40 years and ages ranged from 29 to 54 years. The inclusion criteria for participation were: (1) age of over 25 years, (2) a minimum of 4 pockets with probing pocket depths ≥ 6 mm with at least 3 mm of clinical attachment loss, (3) no periodontal treatment history, (4) proven subgingival infection with \( A. \) actinomycetemcomitans in conjunction with either \( P. \) gingivalis, \( B. \) forsythus and/or \( P. \) intermedia, (5) no abnormalities in stool, (6) no use of systemic antimicrobial therapy in the previous 3 months. All patients who participated in this study consented in writing.

Outline of the study

The outline of the study is shown in Fig. 1. First, a medical history was obtained. Then the deepest, bleeding pocket in each quadrant was selected for clinical and microbiological evaluation (Mombelli et al. 1991, 1994a, Müller et al. 1990). At these 4 experimental sites clinical measurements and microbiological testing was carried out at baseline, after initial periodontal therapy (IT), i.e. 21 weeks after baseline, and after systemic antimicrobial therapy (AM), i.e. 35 weeks after baseline. IT included oral hygiene instructions and supra- and subgingival scaling and root planing for a maximum of 6 hours and was completed within 15 weeks after baseline. At week 21, only oral hygiene was re-inforced. The antimicrobial therapy consisted of amoxicillin 375 mg TID (Flemoxin Solutab\textsuperscript{	extregistered}) and metronidazole 250 mg TID, both drugs for 7 days.

Fig. 1. Study outline.
At week 21, information about the patient's stool was gathered concerning any changes or irregularities in the past 3 months. One week after completion of the antimicrobial therapy, patients were interviewed concerning adverse effects and changes or irregularities of stool. Two questions were asked in order to assess adverse effects using standard phrases (1) "Did anything special occur last week?", (2)" Was there any change in your stool over the past 2 weeks?"

Clinical measurements

To record the responses to clinical therapy the following parameters were employed at the 4 experimental sites.

(1) Plaque index (PI, Sillness & Löe, 1964).
(2) Bleeding index (BI). Bleeding on probing: 0, no bleeding; 1, 'pin prick' bleeding; and 2, immediate and overt bleeding.
(3) Suppuration index (SUP). Suppuration: 0, no suppuration; 1, suppuration.
(4) Probing pocket depth (PPD) using a Hu-Friedy PQW probe.
(5) Clinical attachment level (CAL) by subtraction of the distance between the gingival margin and the cemento-enamel junction from the recorded probing pocket depth.

Microbiological procedures

After removal of supragingival plaque from the 4 experimental sites, a subgingival sample was obtained by using 2 sterile paper points at each site. Paper points from all four experimental sites were pooled and collected in reduced transport fluid (RTF, Syed & Loesche, 1972) and processed within 36 hours (Petit et al. 1991, Van Steenbergen et al. 1993). Tenfold serial dilutions were prepared in RTF and aliquots of 0.1 ml were plated onto 5% horse-blood agar plates (Oxoid no. 2, Basingstoke, England) supplemented with haemin (5 mg/l) and menadione (1 mg/l) for isolation and growth of obligate anaerobic bacteria, and on TSBV for selective isolation and growth of A. actinomycetemcomitans (Slots 1982). Blood agar plates were incubated anaerobically in 80% N2, 10% H2 and 10% CO2 for up to 14 days and TSBV plates were incubated in air + 5% CO2 for 5 days (Van Steenbergen et al. 1986). Blood agar plates were used for enumeration of dark-pigmented colonies and B. forsythus. Representative dark-pigmented colonies were purified and identified using standard techniques (Van Winkelhoff et al. 1985), including Gram-stain, hemagglutination of 3% sheep erythrocytes, fermentation of glucose, production of indole from tryptophan and production of specific enzymes (Van Winkelhoff et al. 1986). B. forsythus was
Additional effects of amoxicillin and metronidazole

identified on the basis of the typical colony morphology, Gram-stain and production of a trypsin-like enzyme (Braham & Moncla 1992).

Statistical analyses

For analyses of the clinical and microbiological data a "patient level response" variable was calculated for each parameter by computing the mean value of the scores assessed at the 4 experimental sites at each assessment. Differences in clinical and microbiological parameters before initial therapy (baseline), after IT and after AM, and between selected patient groups were analyzed using an unpaired Wilcoxon-test. A Fisher's exact test was used to analyze differences in the frequency of species after each phase of therapy. Values of \( p \leq 0.05 \) were accepted as statistically significant.

Results

Clinical effects

The means of the clinical parameters at baseline, after IT and after AM are summarized in Table 1. All clinical parameters improved after IT and showed further improvement after AM with the exception of the PI.

The mean change of PI at the 4 experimental sites decreased 0.4 after IT and increased with 0.2 after AM. The mean BI decreased 0.4 after IT and a further decrease of 0.5 after AM was noted. Suppuration was completely eliminated after systemic antibiotic therapy. The mean change of probing pocket depth after IT amounted 1.4 mm and was further reduced with an additional mean change of 1.1 mm after AM. Clinical attachment gain was 1.1 mm after IT and an additional 0.9 mm was observed after AM.

Microbiological effects of initial periodontal therapy

The frequency of detection of the target bacterial species and the corresponding PPD and CAL on a patient level is summarized in Table 2. One of the 22 A. actinomycetemcomitans patients and 4 of 17 P. gingivalis patients became negative for these species after IT. The number of patients with detectable P. intermedia decreased from 16 to 10 after IT; 2 patients (#12 and 14) became positive for this species. Four of the 14 initially positive patients became negative for B. forsythus after IT. One patient (#12) became positive for B. forsythus after IT. We observed a striking increase in the number of patients with detectable Peptostreptococcus micros (from 4 to 11, \( p \leq 0.05 \)) after IT. Also the number of
Table 1: Mean clinical parameters and standard deviation (SD) at baseline, after initial therapy (IT) and after amoxicillin + metronidazole (AM).

<table>
<thead>
<tr>
<th></th>
<th>Baseline (SD)</th>
<th>After IT (SD)</th>
<th>After AM (SD)</th>
<th>WILCOXON</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=22</td>
<td>I versus II</td>
<td>II versus III</td>
<td>I versus III</td>
</tr>
<tr>
<td>PI</td>
<td>0.5 (0.5)</td>
<td>0.1 (0.2)</td>
<td>0.3 (0.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>BI</td>
<td>1.6 (0.4)</td>
<td>1.2 (0.5)</td>
<td>0.7 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SUP</td>
<td>0.6 (0.3)</td>
<td>0.3 (0.3)</td>
<td>0.0</td>
<td>0.001</td>
</tr>
<tr>
<td>PPD</td>
<td>8.1 (1.2)</td>
<td>6.7 (1.0)</td>
<td>5.6 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAL</td>
<td>8.6 (1.5)</td>
<td>7.5 (1.4)</td>
<td>6.6 (1.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

N: total number of patients; PI: plaque index; BI: bleeding index; SUP: suppuration index; PDD: probing pocket depth; CAL: clinical attachment level.
patients with detectable subgingival *Fusobacterium nucleatum* increased post-therapy (from 3 to 7). All patients but one (#14), positive for *P. micros* and *F. nucleatum*, remained positive after mechanical therapy. The mean PPD and the mean CAL had both significantly improved after IT. Nevertheless, 4 patients showed no clinical attachment gain (#4,6,12,13).

**Microbiological effects of systemic antimicrobial therapy**

All patients completed the systemic antimicrobial therapy. A significant change in the frequency of the selected species was observed after the additional antibiotic therapy. Suppression below detection level was achieved for *A. actinomycetemcomitans* in 18 (p < 0.001) and for *P. gingivalis* in 9 patients (p < 0.001). Of the 14 patients at baseline only one (#18) had detectable levels of *B. forsythus* post-antibiotic therapy. This patient also remained positive for *A. actinomycetemcomitans*. *P. intermedia* was found in 11 of the patients post-antibiotic therapy. *P. micros* and *F. nucleatum* were found at higher frequency after AM (10 and 9, respectively) compared to baseline (4 and 3, respectively). In 7 patients, *P.micros* and in 10 patients *F. nucleatum* were not detected at any time during the study. The mean % recovery of the selected bacteria is summarized in Table 3. Only minor changes in the mean percentages of *A. actinomycetemcomitans* and *P. gingivalis* were observed after initial therapy. By contrast, the mean percentage of *P. intermedia* slightly increased, whereas the mean %’s of *Fusobacterium nucleatum* decreased gradually. Only the mean percentage of *P. micros* declined significantly after mechanical therapy. Two of the 3 patients (#17,22), positive for *A. actinomycetemcomitans* post-antibiotic therapy, had both the highest mean plaque index (1.5) at the end of the study period. Patient #17 had the highest mean plaque index (baseline 2, after IT 1, after AM 1.5) and patient #22 had the highest mean PPD during the entire study (baseline 11 mm, after IT 8.7 mm, after AM 7.5 mm). These 3 *A. actinomycetemcomitans* positive patients also showed significantly higher levels of *P. intermedia* (p ≤ 0.05) during the entire study than the patients who became negative for this species after AM. In retrospect, the 4 patients with detectable levels of *P. gingivalis* post AM had a significantly higher suppuration index after IT (0.2±0.3 versus 0.4±0.3, p=0.04) and showed a higher plaque index (p=0.009), more bleeding on probing (p≤0.0001), deeper probing pocket depth (p=0.03) and more clinical attachment loss (p=0.01) by comparison with the patients without detectable *P. gingivalis* after AM.

On the basis of the microbiological results after AM, the study group was separated into 2 subgroups (Table 4). Group A, representing the patients #1-14 in Table 2, consisted of those subjects who after AM had no detectable levels of *A.
Table 2. Microbiological parameter, probing pocket depth (PPD) and clinical attachment level (CAL) at baseline, after initial therapy (IT) and after amoxicillin + metronidazole (AM) in 22 patients with adult periodontitis.

<table>
<thead>
<tr>
<th>pat. no.</th>
<th>Baseline</th>
<th>After IT</th>
<th>After AM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aa</td>
<td>Pg</td>
<td>Bf</td>
</tr>
<tr>
<td>1</td>
<td>*</td>
<td>-</td>
<td>**</td>
</tr>
<tr>
<td>2</td>
<td>*</td>
<td>**</td>
<td>**</td>
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<tr>
<td>3</td>
<td>**</td>
<td>-</td>
<td>**</td>
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<tr>
<td>4</td>
<td>*</td>
<td>***</td>
<td>-</td>
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<tr>
<td>5</td>
<td>*</td>
<td>-</td>
<td>**</td>
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<tr>
<td>6</td>
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<td>7</td>
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<td>**</td>
<td>-</td>
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<td>8</td>
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<td>-</td>
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<td>9</td>
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<td>*</td>
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<tr>
<td>10</td>
<td>*</td>
<td>**</td>
<td>***</td>
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<tr>
<td>11</td>
<td>*</td>
<td>-</td>
<td>*</td>
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<tr>
<td>12</td>
<td>*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>*</td>
<td>**</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>*</td>
<td>-</td>
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<tr>
<td>15</td>
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<td>**</td>
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<td>16</td>
<td>*</td>
<td>***</td>
<td>-</td>
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<tr>
<td>17</td>
<td>*</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>18</td>
<td>*</td>
<td>*</td>
<td>*</td>
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<tr>
<td>19</td>
<td>*</td>
<td>**</td>
<td>-</td>
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<tr>
<td>20</td>
<td>**</td>
<td>**</td>
<td>-</td>
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<tr>
<td>21</td>
<td>*</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>22</td>
<td>*</td>
<td>**</td>
<td>***</td>
</tr>
</tbody>
</table>

- ND: *: <10%; **: <50%; ***: ≥50%.

Aa: Actinobacillus actinomycetemcomitans; Pg: Porphyromonas gingivalis; Bf: Bacteroides forsythus; Pi: Prevotella intermedia; ND: not detectable.
Table 3. The mean %s, standard deviation (SD), median and ranges of Actinobacillus actinomycetemcomitans (Aa), Porphyromonas gingivalis (Pg), Bacteroides forsythus (Bf), Prevotella intermedia (Pi), Peptostreptococcus micros (Pm) and Fusobacterium nucleatum (Fn) at baseline, after initial treatment (IT) and after amoxicillin + metronidazole (AM).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After IT</th>
<th>After AM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=22</td>
<td>n</td>
<td>mean (SD)</td>
</tr>
<tr>
<td>% Aa</td>
<td>22</td>
<td>21</td>
<td>2.2 (3.2)</td>
</tr>
<tr>
<td>% Pg</td>
<td>17</td>
<td>13</td>
<td>29.1 (27.5)</td>
</tr>
<tr>
<td>% Bf</td>
<td>14</td>
<td>11</td>
<td>21.7 (10.4)</td>
</tr>
<tr>
<td>% Pm</td>
<td>4</td>
<td>11</td>
<td>9.8 (6.3)</td>
</tr>
<tr>
<td>% Fn</td>
<td>3</td>
<td>7</td>
<td>12.6 (7.0)</td>
</tr>
</tbody>
</table>

N: total number of patients, n: number of patients.

#: Change in frequency between baseline and after AM: p< 0.01.
a: Change in percentage between after IT and after AM: p= 0.005.
b: Change in percentage between after IT and after AM: p= 0.02.
c: Change in percentage between after IT and after AM: p= 0.001.
Table 4. Mean clinical parameters in patients, without detectable levels of *A. actinomycetemcomitans*, *P. gingivalis*, *B. forsythus* and <5% *P. intermedia* (group A, n=14) and patients with one of these species and/or ≥ 5% levels of *P. intermedia* (group B, n=8), after systemic antimicrobial therapy.

<table>
<thead>
<tr>
<th>Group</th>
<th>PI (SD)</th>
<th>BI (SD)</th>
<th>PDD (SD)</th>
<th>CAL (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A (SD)</td>
<td>B (SD)</td>
<td>A (SD)</td>
<td>B (SD)</td>
</tr>
<tr>
<td>baseline</td>
<td>0.4 (0.3)</td>
<td>0.7 (0.8)</td>
<td>1.5 (0.4)</td>
<td>1.8 (0.3)</td>
</tr>
<tr>
<td>after IT</td>
<td>0.1 (0.2)</td>
<td>0.2 (0.3)</td>
<td>1.1 (0.5)</td>
<td>1.4 (0.6)</td>
</tr>
<tr>
<td>after AM</td>
<td>0.1 (0.2)****</td>
<td>0.7 (0.5)</td>
<td>0.4 (0.4)**</td>
<td>1.1 (0.5)</td>
</tr>
</tbody>
</table>

PI: plaque index; BI: bleeding index; PPD: probing pocket depth; CAL: clinical attachment loss; SD: standard deviation; n: number of patients; IT: initial therapy; AM: amoxicillin and metronidazole.

* p ≤ 0.03; ** p < 0.005 between groups A and B.
# p = 0.05; ## p ≤ 0.0001 change in group A versus change in group B after AM.
See Table 2: group A, patient nos 1-14; group B, patient nos 15-22.
Additional effects of amoxicillin and metronidazole

actinomycetemcomitans, P. gingivalis, B. forsythus and showed <5% of P. intermedia. Group B showed still presence of one of these 3 species and/or ≥5% levels of P. intermedia. The mean age of group A was 37.5 years and for group B 43.5 years (p=0.05). Group B was characterized by a higher mean PI, BI, PPD and CAL post AM. In retrospect patients in group B showed more loss of clinical attachment at baseline. However, after IT, there were no significant differences in clinical parameters between group A and B. After AM, Group B showed a smaller mean change in PPD and an increase in plaque level.

Adverse effects

All patients reported normal stool at first interview in week 21, i.e. after initial periodontal therapy and before the medication of amoxicillin and metronidazole. After medication, 17 of the 22 patients experienced adverse effects (Table 5). Ten patients reported diarrhoea, one had a more frequent stool but without diarrhoea, 4 patients reported a metallic taste, 4 patients reported headaches and 3 suffered from nausea. The reported events were mild and were tolerated by all patients. The adverse effects were deemed to relate to the medication.

Discussion

In this study, we investigated the clinical and microbiological effects of initial periodontal therapy in patients with A. actinomycetemcomitans-associated adult periodontitis and the additional effects of a systemic amoxicillin plus metronidazole therapy.

All clinical parameters improved significantly after the initial periodontal therapy. The mean change in clinical attachment level (1.1 mm) concurs with other studies, while the observed 1.4 mm mean reduction in probing pocket depths in this study was moderate (Cobb 1996, Hämmerle et al. 1991, 2.1 mm and 2.2 mm, respectively). A minimal clinical improvement in adult periodontitis patients after initial periodontal therapy has been related to subgingival persistence of A. actinomycetemcomitans and P. gingivalis (Mombelli et al. 1994 a,b, Renvert et al. 1990 a,b, Ali et al. 1992). These observations may, in part, explain our results. However, due to the selection criteria, the evaluated sites may have comprised a relative large number of angular bony defects of which it has been shown that gingival recession will occur to a limited extent (Hellström et al. 1996). The moderate effects of the initial periodontal therapy on the subgingival microflora cannot be explained by poor supragingival plaque control since a significant reduction of the PI after IT (from 0.5 to 0.1) was achieved in the present study population.
Table 5. Adverse effects after amoxicillin and metronizole in 22 patients with adult periodontitis.

<table>
<thead>
<tr>
<th>Adverse events n=17</th>
<th>Severity</th>
<th>No. of days of adverse effects mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>steel taste</td>
<td>4 mild</td>
<td>5.2 (2–7)</td>
</tr>
<tr>
<td>headache</td>
<td>4 mild-moderate</td>
<td>7.7 (3–14)</td>
</tr>
<tr>
<td>nausea</td>
<td>3 moderate</td>
<td>10.0 (2–14)</td>
</tr>
<tr>
<td>diarrhoea</td>
<td>10 mild</td>
<td>4.9 (2–14)</td>
</tr>
<tr>
<td>burning tongue</td>
<td>1 mild</td>
<td>14</td>
</tr>
<tr>
<td>dry mouth</td>
<td>1 moderate</td>
<td>5</td>
</tr>
<tr>
<td>erythema</td>
<td>1 moderate</td>
<td>14</td>
</tr>
</tbody>
</table>

n: no. of patients.
The rationale for continuing periodontal therapy is based on observations that suggest further disease progression when *A. actinomycetemcomitans*, *P. gingivalis* and *P. intermedia* are still detectable after initial periodontal therapy (Ali et al. 1992, Bragd et al. 1987, Dahlén et al. 1996, Goené et al. 1990, Wennström et al. 1987). The choice for periodontal antimicrobial therapy was based on earlier observations showing that renewed debridement has little or no additional effect (Badersten et al. 1984). In this study the periodontal therapy was followed by an additional systemic antimicrobial therapy with amoxicillin plus metronidazole. The choice of this systemic antibiotic regime was based on an earlier report showing predictable and long-term suppression of subgingival *A. actinomycetemcomitans* and *P. gingivalis* (Pavić et al. 1994).

The results of the additional course of amoxicillin and metronidazole showed a significant further reduction in mean probing pocket depth, bleeding tendency, suppuration, and gain of clinical attachment level. By comparison with the baseline measurements, the reduction of PPD (2.5 mm) and gain of CAL (2 mm) 3 months after IT followed by AM, exceeded those reported by Pavić and co-workers 1994 (2.3 mm and 1.4 mm, respectively). In the present study the clinical improvements were paralleled by a major reduction in the isolation frequency of *A. actinomycetemcomitans*, *P. gingivalis*, and *B. forsythus*. Especially the reduction of *B. forsythus* in positive patients was noteworthy and has not previously been reported.

Not all patients were free of putative pathogens after the antibiotic therapy. To study the additional effects of antibiotics, no attempt was made to disrupt the subgingival biofilm shortly before the antibiotic therapy was commenced. Therefore, our treatment may not have been the most effective therapy. The recent recognition that subgingival plaque is in fact a biofilm in which subgingival bacteria greatly increase their resistance to antibiotics, may explain that some patients still had detectable levels of periodontal pathogens after therapy (Anwar et al. 1992, Darveau et al. 1997, Van Winkelhoff et al. 1994, Wright et al. 1997).

On the basis of the microbiological data after systemic antimicrobial therapy, the study population was divided into 2 subgroups. Group A, patients without *A. actinomycetemcomitans*, *P. gingivalis*, *B. forsythus* and < 5% *P. intermedia*, and group B, patients with one or more of these periodontal pathogens and ≥ 5% *P. intermedia* (Wennström et al. 1987). After AM, group B had significantly higher PI, BI, PPD and CAL scores then group A. In retrospect, group B had significantly more clinical attachment loss at baseline than group A. However, after IT, no significant differences were noted between the 2 subgroups; thus group B responded better to IT than group A. This concurs with the studies of Badersten et al. (1984) and Cobb (1996) who showed that greater gain of clinical attachment...
and greater reduction of pocket depth can be expected in deeper than in shallower sites after IT. By contrast, after AM the most pronounced improvement of clinical parameters was noted in group A, the patients with no detectable levels of A. actinomycetemcomitans, P. gingivalis, B. forsythus and < 5% P. intermedia. The difference in plaque scores after AM in group A as opposed to group B needs further discussion. Several studies have shown that the rate of plaque accumulation is related to the degree of gingival inflammation, i.e. the more gingivitis, the more rapid plaque formation (Hillam & Hull 1977, Ramberg et al. 1995, 1996). This phenomenon may be explained by the persistence of subgingival periodontal pathogens which results in an increase of gingival crevicular fluid (Giedrys-Leeper et al. 1985) which in turn provides a rich source of nutrients for plaque formation (Darveau et al. 1997). In this respect it is important to note that certain extracellular proteases of especially P. gingivalis are able to increase vascular permeability (Imamura et al. 1994). Consequently, the higher plaque scores after AM in group B compared to group A may not be the result of a different quality of oral hygiene control but may be attributed to the presence of subgingival periodontal microflora and continuing inflammatory response.

The aim of periodontal therapy may be defined as creating a periodontal condition which shows a long-term stable attachment level. In this respect, it seems likely that group A fulfilled the conditions to achieve this goal since the patients involved showed low plaque scores and no detectable periodontal pathogens, and this has been associated with a stable long-term periodontal condition (Dahlén et al. 1996, Wennström et al. 1987). Consequently, group B did not reach the endpoint of active periodontal treatment and will probably need additional periodontal therapy (Haffajee et al. 1997, Rams et al. 1996, Slots 1996, Winkel et al. 1997).

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Additiona ll effect s  o f amoxicilli n  an d  metronidazol e

References


temcomitans, Bacteroides gingivalis and Bacteroides intermedius to indicate progressive periodontitis; a retrospective study. *Journal of Clinical Periodontology* 14, 95-99.


Additional effects of amoxicillin and metronidazole


Chapter 6


