Accepted Article

Treatment of rosacea and demodicosis with benzyl benzoate: effects of different doses on Demodex density and clinical symptoms

Running head: Benzyl benzoate to treat rosacea and demodicosis

Key words: Demodex; rosacea; demodicosis; benzyl benzoate; crotamiton; standardized skin surface biopsy.

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Publishable disclosure statement:
This article has no funding sources.
Dr Forton occasionally works as a consultant for Galderma.
Prof De Maertelaer has no conflicts of interest to declare.
Contents of the manuscript have not been previously published and are not currently submitted elsewhere.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jdv.15938
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ABSTRACT

**Background:** Patients with rosacea or demodicosis have high facial skin Demodex densities (Dds). Topical ivermectin, benzyl benzoate (BB) and crotamiton have been shown to decrease Dds in vivo, but there are few data on the clinical and acaricidal effects of BB among patients with rosacea.

**Objective:** To evaluate the impact of topical BB (+crotamiton) treatment on Dds and clinical symptoms of rosacea and demodicosis, and compare three BB treatment regimens.

**Methods:** In this retrospective observational study, 394 patients (117 with rosacea, 277 with demodicosis) were included. Three BB (+crotamiton) treatment regimens were compared: 12% once daily, 12% twice daily and 20% once daily. Dds were measured using two consecutive standardized skin surface biopsies (superficial [SSSB1] and deep [SSSB2]) before treatment and at the first follow-up. Symptoms were evaluated using investigator global assessment. Treatment was considered effective if the Dd had normalized (SSSB1 ≤5 D/cm² AND SSSB2 ≤10 D/cm²) or symptoms had cleared and curative if the Dd had normalized and symptoms had cleared.

**Results:** At an average of 2.7 months after treatment start, the total Dd (SSSB1+2) had decreased by 72.4±2.6% from the initial value across the whole cohort. Dds had normalized in 139 patients (35%) and symptoms had cleared in 122 (31%). Treatment was effective in 183 (46%) patients and curative in 78 (20%). Compliance was good: 77% of patients correctly followed treatment instructions. Results were similar in patients with rosacea and those with demodicosis. The 12% once daily regimen was less effective than the other doses, and had poorer compliance than the 12% twice daily regimen.
**Conclusion:** Topical treatment with BB (+crotamiton) may be an effective treatment for rosacea as well as demodicosis, indirectly supporting a key role of the mite in the pathophysiology of rosacea. The two higher dose regimens were more effective than the lower dose.

**INTRODUCTION**

Rosacea and demodicosis are common dermatoses affecting about 10% of the population.\(^1,2\) Although still controversial,\(^3-5\) evidence supporting a role of Demodex in papulopustular rosacea (PPR) is accumulating,\(^6-10\) and recent guidelines for the treatment of rosacea include use of ivermectin, an acaricidal drug, as a first-line topical treatment for PPR.\(^11-13\)

In 1998, we demonstrated an acaricidal action on *Demodex folliculorum* of benzyl benzoate (BB) and, to a lesser extent of crotamiton,\(^14\) treatments that have been poorly studied.\(^5,15\) In the present study, we analyzed the impact of three topical BB (with crotamiton) treatment regimens on the evolution of Demodex densities (Dds) and clinical symptoms in patients with demodicosis and rosacea.

**METHODS**

This study is a retrospective subanalysis of some patients included in an earlier study,\(^9\) and was approved by the Erasme Hospital Ethics committee. Patients with rosacea with centro-facial papulopustules or with demodicosis were included if they had no associated facial dermatosis, had received BB but no anti-inflammatory treatment (e.g., tetracyclines or metronidazole) and had attended follow-up. Only the first follow-up visit, generally scheduled for two months after the initial consult, was analyzed.
At the initial consultation and at follow-up, each patient had two consecutive standardized skin surface biopsies (SSSBs) performed, allowing measurement of two Dds (D/cm²) (superficial [SSSB1] and deep [SSSB2]). The SSSBs were performed at the same site at initial consultation and follow-up.

During the study period (2002-2010), dosages and frequency of application of the BB cream and excipients were altered to improve compliance and efficacy, giving three groups:

1. BB12% 1x/d: a cream composed of crotamiton 10% applied in the morning and another composed of BB 12% and crotamiton 10% in the evening. Different excipients were used including carbopol gel, cetyl ic cream, cosmetic moisturizer and Therapeutic Magistral Form (TMF) cetomacrogol cream.

2. BB12% 2x/d: BB 12% and crotamiton 10% twice a day in TMF cetomacrogol cream.

3. BB20% 1x/d: moisturizing cream in the morning and 20 to 24% BB with 10% crotamiton in TMF cetomacrogol cream in the evening.

Patients were instructed to wash the face twice daily using a mild soap and a flannel and to apply the topical cream over the face and neck, avoiding the eye area and the lips.

The effects of the different treatments were evaluated by the change in Dd from initial consultation and the presence or absence of symptoms, assessed using investigator global assessment (IGA). Treatment was considered effective if the Dd had normalized (SSSB1 ≤5 D/cm² AND SSSB2 ≤10 D/cm²) OR symptoms had cleared, and curative if the Dd had normalized AND symptoms had cleared.

Compliance was considered good if the patient stated he/she had correctly followed treatment instructions.
Differences in continuous variables were compared between groups using an analysis of covariance (ANCOVA), including age and sex as covariates, followed by Sidak tests for multiple comparisons if required. In the absence of age and sex effects, continuous variables were compared using classical Student t-tests or Welch’s t-tests in case of variance inequality, or with analyses of variance (ANOVA) followed by Sidak or Dunnett T3 multiple comparison tests when required according to the results of the Levene test for homoscedasticity. Differences in qualitative variables were compared using Pearson’s exact chi-square tests.

RESULTS
A total of 394 patients were included in the analysis (Table 1): 277 with demodicosis and 117 with rosacea with papulopustules (105 with and 11 without persistent erythema, and 1 steroid-induced rosacea). Mean age was 47.5±0.8 years (range: 7.4-90.5); 278 were women. The cheek was the most frequent biopsy site (336/394). In the 12% 1x/d group, the excipients were carbopol gel, cetylic cream, TMF cetomacrogol cream and cosmetic cream for 18, 20, 38 and 119 patients, respectively. The mean time between the initial consultation and the follow-up was 2.7±0.2 months (range: 0.2-65.2).

There were no statistically significant differences between the three treatment groups in terms of diagnosis, mean age, biopsy site, duration between visits or initial Dds. There were more women in the BB12% 1x/d group than in the BB20% 1x/d group (Table 1), but the statistical method used for comparisons corrected for these differences. The mean follow-up Dds were significantly lower than the initial values for the whole cohort (SSSB1: 25±2 vs 94±6 D/cm²; SSSB2: 37±3 vs 208±10 D/cm²; both p<0.001) and within each treatment group (Table 1, Fig. 1), with no significant
differences according to sex or clinical diagnosis. In the whole cohort, the total Dd (SSSB1+2) decreased by 72.4±2.6% from the initial value (Table 1).

At follow-up, Dds had normalized in 35% of patients and symptoms had cleared in 31% (Table 1), with no significant differences according to clinical diagnosis. Treatment was effective in 46% of patients and curative in 20% (Table 1, Figs 2, 3). Symptom clearance was more frequently observed in men (34%) than in women (20%) (p=0.041). Among the 44 patients in whom symptoms had cleared but Dd had not normalized, the Dd had decreased significantly (SSSB1: from 109±21 to 20±3 D/cm² [p<0.001]; SSSB2: from 259±42 to 21±2 D/cm² [p<0.001]).

Treatment was less effective in the BB12% 1x/d group, with fewer patients having cleared symptoms than in the other two treatment groups, and fewer patients having normalized Dds than in the BB12% 2x/d group (Table 1).

Compliance was good in 77% of the patients (Table 1). There was 65% concordance between compliance and effectiveness of treatment.

DISCUSSION

Topical treatment with BB (with crotamiton) was effective at reducing Dds and clearing clinical symptoms, in rosacea as well as demodicosis. When comparing the three treatment regimens, the 12% 1x/d regimen was clearly less effective than the two other regimens. The differences between the 12% 2x/d and 20% 1x/d regimens were less obvious, the only statistically significant difference being in the percentage of patients who only had cleared symptoms (without normalization of their Dd). The lack of significant differences for the other results may be because of the small number of patients in the BB20% 1x/d group, thus limiting the statistical power.
In an earlier study, we observed a small degree of acaricidal action of crotamiton, so we always prescribe this in combination with BB.\textsuperscript{14} In the first two groups (BB12% 1x/d and 2x/d), crotamiton was applied twice a day, but there was still a clear difference in favor of the twice daily application of BB12%. Moreover, the third application mode, in which crotamiton was applied only once a day, was as effective as the twice daily application of BB12% (with crotamiton). These observations suggest that the main acaricidal effects were caused by BB and not crotamiton.

Interestingly, compliance was better in the BB12% 2x/d group than in the BB12% 1x/d group, despite the known irritating properties of BB: this may be related to the fact that compliance and effective treatment were related. Moreover, compliance in the BB20% 1x/d group was not significantly different to the compliance in the BB12% groups despite the higher concentration of BB. This observation may be explained by the fact that these patients used a moisturizing cream in the morning, potentially easing the irritating action of the BB, and also by the small number of patients in this group.

Topical ivermectin, with its anti-inflammatory and direct killing action on mites,\textsuperscript{16} has been proposed for the treatment of PPR since 2014.\textsuperscript{11-13,16,17} In our practice, we have observed that patients are less tolerant of BB regimens than of ivermectin. Nevertheless, BB is considerably cheaper and could be useful for patients allergic to ivermectin or when ivermectin is not available.

Of note, BB has no anti-inflammatory action (unlike ivermectin), and may potentially have pro-inflammatory effects, causing skin irritation. Its therapeutic effects are therefore attributable solely to its acaricidal action. Our observation that
BB is an effective treatment in rosacea as well as in demodicosis, thus strongly supports a key role of the mite in rosacea.

In some patients, symptoms cleared but Dds did not normalize: this observation may be explained by the fact that symptoms (particularly more discreet ones, such as follicular scales) can resolve when the Dd decreases, even if not yet normalized, as in subclinical demodicosis.\textsuperscript{18}

Our study has several limitations including its retrospective nature; the small number of patients in the BB20\% 1x/d group; the different excipients used in the BB12\% 1x/d group and the range of BB concentrations for the BB20\% 1x/d group; the reliance on patient statement for assessment of compliance; and the use of dichotomous IGA and not grades\textsuperscript{19,20} to assess symptom evolution. Moreover, as the majority of patients with PPR in our practice have mild to moderate rosacea, results may be different in patients with more severe PPR.

In conclusion, after an average treatment period of just 2.7 months, topical application of BB (with crotamiton) was effective at reducing Dds and clearing clinical symptoms, not only in demodicosis but also in rosacea with papulopustules, indirectly supporting a key role of the mite in the pathophysiology of rosacea. Among the three application modes, the two higher dose regimens (BB20\% 1x/d and BB12\% 2x/d) were more effective than the lower dose (BB12\% 1x/d), with similar or better compliance.
ACKNOWLEDGEMENTS

We thank Prof M Parmentier, Prof V. del Marmol, and Prof C Verhoeven, for their constructive remarks, Dr K Pickett for proofreading, and our patients for agreeing to participate in the study.

REFERENCES


TABLES

Table 1 Demographic data and effects of the acaricidal treatment in the whole cohort and in the three treatment groups: Demodex densities, clinical symptoms and compliance.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Treatment groups</th>
<th>BB12% 1x/d</th>
<th>BB12% 2x/d</th>
<th>BB20% 1x/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>394</td>
<td>195</td>
<td>171</td>
<td>28</td>
<td></td>
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<tr>
<td>Age : years Mean±SEM</td>
<td>47.5±0.8</td>
<td>48.1±1.0</td>
<td>47.1±1.2</td>
<td>45.1±3.1</td>
<td></td>
</tr>
<tr>
<td>Number of women (%)</td>
<td>278 (71)</td>
<td>150 (77)</td>
<td>113 (66)</td>
<td>15 (54)</td>
<td></td>
</tr>
<tr>
<td>SSSB1 : number of Demodex/cm²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial mean±SEM</td>
<td>94±6</td>
<td>88±8</td>
<td>103±19</td>
<td>78±19</td>
<td></td>
</tr>
<tr>
<td>Follow-up mean±SEM</td>
<td>25±2</td>
<td>28±3</td>
<td>23±4</td>
<td>22±6</td>
<td></td>
</tr>
<tr>
<td>Decrease mean±SEM</td>
<td>69±5</td>
<td>80±9</td>
<td>56±19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSSB2 : number of Demodex/cm²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial mean±SEM</td>
<td>208±10</td>
<td>188±13</td>
<td>221±16</td>
<td>259±49</td>
<td></td>
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<tr>
<td>Follow-up mean±SEM</td>
<td>37±3</td>
<td>45±4</td>
<td>28±4</td>
<td>40±15</td>
<td></td>
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<tr>
<td>Decrease mean±SEM</td>
<td>170±10</td>
<td>134±12</td>
<td>193±15</td>
<td>219±50</td>
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<tr>
<td>SSSB1+2 % decrease from initial</td>
<td>72.4±2.6</td>
<td>63.1±4.8</td>
<td>82.6±1.9</td>
<td>74.5±6.3</td>
<td></td>
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<tr>
<td>% normalized Dd (n)</td>
<td>35 (139)</td>
<td>24 (47)</td>
<td>49 (83)</td>
<td>32 (9)</td>
<td></td>
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<tr>
<td>% cleared symptoms (n)</td>
<td>31 (122)</td>
<td>20 (38)</td>
<td>40 (69)</td>
<td>54 (15)</td>
<td></td>
</tr>
<tr>
<td>% ONLY normalized Dd (n)</td>
<td>15 (61)</td>
<td>13 (26)</td>
<td>19 (32)</td>
<td>11 (3)</td>
<td></td>
</tr>
<tr>
<td>% ONLY cleared symptoms (n)</td>
<td>11 (44)</td>
<td>9 (17)</td>
<td>11 (18)</td>
<td>32 (9)</td>
<td></td>
</tr>
<tr>
<td>% cured (n)</td>
<td>20 (78)</td>
<td>11 (21)</td>
<td>30 (51)</td>
<td>21 (6)</td>
<td></td>
</tr>
<tr>
<td>% effective Treatment (n)</td>
<td>46 (183)</td>
<td>33 (64)</td>
<td>59 (101)</td>
<td>64 (18)</td>
<td></td>
</tr>
<tr>
<td>% good compliance (n)</td>
<td>77 (304)</td>
<td>71 (138)</td>
<td>85 (146)</td>
<td>71 (20)</td>
<td></td>
</tr>
</tbody>
</table>

The circles indicate the groups being compared; green lines show comparisons across three groups, red lines comparisons between two groups. Vertical comparisons: follow-up versus initial densities. Only statistically significant p values are shown.

The changes in SSSB1 and 2 showed similar patterns. The decrease in SSSB2 was different across the 3 groups, although the differences were NS when the groups were compared two by two. This finding may be the result of a lack of power of the test because of the large variability in the initial SSSB2 values in the BB20% 1x/d group and the small number of patients in this group. Indeed, when the two higher dose treatments (showing similar decreases) were combined, the mean decrease in SSSB2 was significantly greater than in the BB12% 1x/d group.
FIGURE LEGENDS

Fig 1  Initial and follow-up Demodex densities (SSSB1 and SSSB2) in the three treatment groups. There was no statistically significant difference among the groups in initial SSSB1 or SSSB2, in follow-up SSSB1, or in the decrease in SSSB1. The follow-up SSSB2 was lower in the BB12% 2x/d group than in the BB12% 1x/d group (p=0.027).

SSSB: Standardized Skin Surface Biopsy; BB: benzyl benzoate.

Fig 2  Percentages of patients (number of patients in brackets) with effective treatment (normalization of the Demodex density [Dd] OR symptoms cleared) and cure (normalization of the Dd AND symptoms cleared). When comparing the three treatment regimens, the once a day application of 12% BB was less effective than the twice a day application and than the 20% once daily regimen. The 20% BB treatment appeared a little more effective than the 12% twice daily, but the only statistically significant difference was for the percentage of patients who only had cleared symptoms (without normalization of the Dd).

0 Sympt only: patients with symptoms cleared but with Dd not normalized.

Normal Dd only: patients with normalized Dd but still with symptoms.

Normal Dd AND 0 Sympt: patients with normalized Dd and with symptoms cleared.

The circles indicate the subgroups concerned by the comparisons; green lines show comparisons across three groups, red lines comparisons between two groups. ***: p<0.001; (a): p=0.003. Only statistically significant p values are shown.
Fig 3  Papulopustular rosacea: evolution with topical treatment.

Right cheeks of two patients with papulopustular rosacea. The successive standardized skin surface biopsy (SSSB1+SSSB2) values are indicated on the figures. Patients’ permissions obtained. These patients, seen recently, were not included in the study.

(a): A 38-year old woman with papulopustular rosacea for 1 year. She was prescribed BB12% 1x/d.

(b): Two months later, the Demodex density had normalized and symptoms were reduced although not completely cleared: follicular scales and papules had disappeared but residual erythema persisted where the papulopustules had been present. According to the investigator global assessment, her symptoms were therefore considered as “not cleared”.

(c): Papulopustular rosacea: A 69-year old patient with papulopustular rosacea for 3 years, with blepharitis and conjunctivitis; he had already seen 3 dermatologists and received many treatments (tetracyclines, oral and topical metronidazole, anti-redness creams, corticosteroids, preparation with crotamiton, erythromycin, metronidazole and ketoconazole, …) without success. We prescribed BB20% 1x/d and treatment for the eyelashes (washing lotion and fucidic acid ophthalmic ointment 2x/d).

(d): Two months later, the patient was cured: his Demodex density had normalized and his symptoms (follicular scales and papules) had cleared.