Ethyl lactate and benzoyl peroxide in acne vulgaris

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Synopsis
In a double-blind study involving patients with mild to moderately severe acne vulgaris, a 2.5% Benzoyl Peroxide formulation was compared with a 5% Ethyl Lactate anhydrous gel, with a Benzoyl Peroxide-Ethyl Lactate Gel and with a new vehicle. This new vehicle seems to develop a considerable antiseborrheic activity per se, since it reduces the «casual level» by some 10% (p<0.05) after two weeks of therapy, gradually reaching 40% (p<0.01) after three months of continuous use.

The 2.5% Benzoyl Peroxide formulation showed to be more effective than the 5% Ethyl Lactate Gel, but less effective than Benzoyl Peroxide-Ethyl Lactate Gel in reducing the number of papules and pustules. Both Benzoyl Peroxide and Benzoyl Peroxide-Ethyl Lactate formulations significantly reduced propionibacterium acnes and free fatty acid percentage in surface lipids after 2.5 weeks of topical use.

On the contrary, Ethyl Lactate alone showed only a bacteriostatic activity, whereas, in compounds, it appears to be capable of strengthening the effect of the sole Benzoyl Peroxide.

Desquamation, erythema and symptoms of burning were observed only with benzoyl Peroxide formulations.

Finally, what is to be noticed is the exceptionally interesting activity of this new anhydrous vehicle consisting of a highly volatile special lipidic mixture. This vehicle results to be able to strongly reduce surface lipidic films and, at the same time, it facilitates the penetration of both Ethyl Lactate and Benzoyl Peroxide through the pilo-sebaceous ducts.
Riassunto
Nel corso di uno studio a doppio cieco su pazienti con acne vulgaris da leggera a moderatamente severa, si è comparata una formulazione al 2,5% di perossido di benzoile con un gel anidro al 5% di lattato di etile, un gel di lattato di etile e perossido di benzoile e un nuovo veicolo.
Tale veicolo sembra sviluppare una considerevole attività antiseborroica, poiché riduce il «livello occasionale lipidico» di circa il 10% (p<0,05), arrivando progressivamente al 40% (p<0,01) dopo tre mesi di uso continuato.
La formulazione al 2,5% di perossido di benzoile si è dimostrata più efficace del gel di lattato di etile al 5%, ma meno del gel di lattato di etile e perossido di benzoile, nel ridurre il numero di papule e pustule. Sia la formulazione di perossido di benzoile che quella di lattato di etile e perossido di benzoile hanno ridotto significativamente il numero di propionibatteri, nonché la percentuale di acidi grassi liberi nei lipidi di superficie, dopo 2,5 settimane di applicazione locale. Il lattato di etile solo ha dimostrato di possedere, al contrario, un'attività batteriostatica, mentre sembra essere in grado di rafforzare l'attività del perossido di benzoile. Disquamazioni, eritemi e sintomi di bruciature sono stati notati solo con le formulazioni di perossido di benzoile.
In conclusione, ciò che si rivela di eccezionale interesse è l'attività svolta da questo nuovo veicolo anidro, composto da una speciale miscela lipidica altamente volatili, che sembra in grado di ridurre energicamente il mantello lipidico di superficie e, allo stesso tempo, di facilitare la penetrazione sia del lattato di etile che del perossido di benzoile, attraverso i dotti pilo-sebacei.

Resmen
En un estudio doble ciego sobre pacientes con acné vulgaris de leve hasta moderadamente severa, se ha comparado una formulación de 2,5% de peróxido de benzoilo con un gel anhidro de 5% de lactato de etilo, con un gel de lactato de etilo y peróxido de benzoilo y con un nuevo vehiculo.
Ese nuevo vehiculo parece desarrollar por si mismo una considerable actividad anti-seborrea, ya que reduce el «nivel casual» de más o menos el 10% (p<0,05) después de dos semanas de tratamiento, llegando gradualmente al 4*% (p<0,01) después de tres meses de uso continuo. La formulación de 2,5% de peróxido de benzoilo se ha probado más eficaz que el gel de 5% de lactato de etilo, pero menos eficaz que el gel de lactato de etilo y de peróxido de benzoilo en reducir el número de púpulas y pústulas.
Tanto la formulación de peróxido de benzoilo como la de lactato de etilo y de peróxido de benzoilo redujeron significativamente la acné de propionibacterias y el porcentaje de ácidos grasos libres en los lípidos de superficie después de 2,5 meses de aplicación tópica. Al contrario, el lactato de etilo solo ha manifestado una actividad bacteriostática solamente, mientras que, en los compuestos, parece ser capaz de reforzar el efecto del peróxido de benzoilo. Descarnaciones, eritemas y síntomas de quemaduras se han observado sólo con las formulaciones de peróxido de benzoilo. En fin, lo que hay que notar es la actividad sumamente interesante de ese nuevo vehiculo anhidro que consiste en una especial mixtura lipídica altamente volátil. Ese vehiculo resulta capaz de reducir fuertemente la película lipídica de superficie y, a la vez, facilita la penetración tanto del lactato de etilo como del peróxido de benzoilo a través de los conductos pilo-sebáceos.
Résumé
Dans une étude double aveugle sur des patients avec l'acné vulgaris, de sa forme légère jusqu'à une forme modérément sévère, une comparaison a été effectuée entre une formulation à 2,5% de peroxyde de benzoyle et un gel anhydre à 5% de lactate d'éthyle et peroxyde et un nouveau véhicule. Le véhicule semble donner lieu à une activité antiseborrhéique remarquable, car il réduit le «niveau casuel» d'environ 10% après trois mois d'emploi continu. La formulation à 2,5% de peroxyde de benzoyle s'est révélée plus efficace que le gel de lactate d'éthyle et peroxyde de benzoyle, dans la réduction du nombre de papules et pustules. Aussi bien la formulation de peroxyde de benzoyle pour la formulation de lactate d'éthyle et peroxyde de benzoyle ont réduit d'une façon significative l'acné causée par les propionbactéries, ainsi que le pourcentage d'acides gras libres dans les lipides de surface après 2,5% semaines l'application locale. Au contraire, le lactate d'éthyle tout seul n'a démontré qu'une activité bactériostatique, tandis que quand il est combiné, il semble pouvoir renforcer l'effet du peroxyde de benzoyle. Les desquamations, les érythèmes et les symptômes de brûlures n'ont été remarqués qu'avec les formulations de peroxyde de benzoyle. En conclusion, ce qui se révèle très intéressant, c'est l'activité de nouveau véhicule anhydre composé par un mélange lipidique spécial très volatile. Le dernier est à même de réduire énergiquement la pellicule lipidique superficielle et, en même temps, de faciliter la pénétration aussi bien du lactate d'éthyle que du peroxyde de benzoyle par les canaux pilo-sébacés.

Synopse
Introduction

Benzoyl Peroxide and Ethyl Lactate are both used as active principles for the treatment of acne vulgaris (1-4). Ethyl Lactate is used, without any problems, at concentrations of 10%, whereas Benzoyl Peroxide is generally used at concentrations of 5, 10 and 20%. The higher concentrations, however, are frequently associated with irritative and desquamative side effects (6-10). Furthermore, the activity of both Ethyl Lactate and Benzoyl Peroxide always directly depends upon the type of vehicle used. Recent studies have demonstrated that when the concentration of Benzoyl Peroxide is reduced to 25%, similar therapeutic results can be obtained in terms of reduction of inflammatory lesions of acne, while markedly decreasing the irritative effect (11).

The present study is aimed at controlling the activity of 5% Ethyl Lactate, of 2.5% Benzoyl Peroxide and of a combination of both these components when incorporated into a special anhydrous vehicle. In order to define the activity of these formulations, sixty patients suffering from acne vulgaris were examined with regard to the total number of inflammatory lesions, and the total quantity of sebum and fatty acids in the horny layer.

Materials and methods

Materials:
Formula 1: Special anhydrous vehicle.
Formula 2: Vehicle + 5% Ethyl Lactate.
Formula 3: Vehicle + 2.5% Benzoyl Peroxide.
Formula 4: Vehicle + 5% Ethyl Lactate + 2.5% Benzoyl Peroxide.

Equipment:
Sebumeter SM 410.

Clinical Study

Sixty voluntary subjects (30 men and 30 women) aged from 14 to 25 years, who had all been suffering from polymorphous acne vulgaris for a period ranging from 8 months to 6 years, were subjected to experimentation. All the subjects, divided into three groups of twenty persons each, were given two small jars of cream. The creams given to the groups were labeled as follows: formula 1 and formula 2, were given to the first group; formula 1 and formula 3, were given to the second group; formula 1 and formula 4, were given to the third group. The contents of the jars was known neither by the voluntary patients, nor by the researchers. All the subjects were given detailed instructions — twice daily each washed their faces with a special non — medicated glycerine soap, rinsed with normal water and dried with a cotton towel. They then applied the two creams under examination, the first formula being applied on the right cheek and the second formula on the left cheek. This was continued, morning and evening, for twelve weeks. Four weeks before starting the experiment, the subjects suspended all pharmaceutical or cosmetic treatments, both topically and systemically. All the subjects were checked before starting the experiment and at 2, 4, 6, 8, 10 and 12 weeks. The acne lesions were checked in a specified area of 9 cm², both on the right and on the left cheek. Comedones, microcysts, pustules and nodules were quantified by separately calculating them by means of a transparent millimeter grid of cellophane. The resulting data are shown in Tables I-III and Figures 1-3. At each evaluation the presence of erythema at various intensities was also observed, with or without evident desquamation, and each observation was given a score as per the following scheme:
Table I
Comparison of effect of 5% ethyl lactate and vehicle

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Number of subjects</th>
<th>Comedones and Microcysts (Mean N.)</th>
<th>Mean % Reduction</th>
<th>Pustules and Nodules (Mean N.)</th>
<th>Mean % Reduction</th>
<th>Sebumeter Lectures</th>
<th>Mean % Reduction</th>
<th>5% Ethyl lactate</th>
<th>Special anhydrous vehicle</th>
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<td>—</td>
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<td>—</td>
<td>189</td>
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<td>4</td>
<td>20</td>
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<td>12.8</td>
<td>10.5</td>
<td>14.6</td>
<td>160</td>
<td>15.1</td>
<td>17.6</td>
<td>6.2</td>
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<td>19.1</td>
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<td>9.0</td>
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<td>58.0</td>
<td>8.1</td>
<td>34.0</td>
<td>101</td>
<td>45.7</td>
<td>16.0</td>
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Table II
Comparison of effect of 2.5% benzoyl peroxide and vehicle

<table>
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<tr>
<th>Weeks</th>
<th>Number of subjects</th>
<th>Comedones and Microcysts (Mean N.)</th>
<th>Mean % Reduction</th>
<th>Pustules and Nodules (Mean N.)</th>
<th>Mean % Reduction</th>
<th>Sebumeter Lectures</th>
<th>Mean % Reduction</th>
<th>2.5% Benzoyl peroxide</th>
<th>Special anhydrous vehicle</th>
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<td>15.7</td>
<td>22.1</td>
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<td>14.1</td>
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<td>60.3</td>
<td>97.8</td>
<td>44.3</td>
<td>19.8</td>
<td>7.5</td>
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<td>7.3</td>
<td>66.9</td>
<td>3.6</td>
<td>68.7</td>
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<td>18.2</td>
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<td>69.0</td>
<td>2.8</td>
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<td>76.7</td>
<td>56.3</td>
<td>17.4</td>
<td>18.5</td>
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### Table III
**Comparison of effect of 5% ethyl lactate + 2.5% benzoyl peroxide and vehicle**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Number of subjects</th>
<th>Benzoyl peroxide + Ethyl lactate</th>
<th>Special anhydrous vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Countedones and Microcysts (Mean N.)</td>
<td>Mean % Reduction</td>
</tr>
<tr>
<td>0</td>
<td>20</td>
<td>20.8</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>13.5</td>
<td>35.1</td>
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<td>20</td>
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<td>48.0</td>
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<td>20</td>
<td>8.2</td>
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<td>8</td>
<td>20</td>
<td>6.4</td>
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<td>10</td>
<td>20</td>
<td>5.8</td>
<td>72.1</td>
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<tr>
<td>12</td>
<td>20</td>
<td>5.0</td>
<td>76.2</td>
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</table>

### Table IV
**Frequency of erythema and peeling**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Special Anhydrous Vehicle (Score FORMULA 1)</th>
<th>Vehicle + 5% Ethyl Lactate (Score FORMULA 2)</th>
<th>Vehicle + 2.5% Benzoyl Peroxide (Score FORMULA 3)</th>
<th>Vehicle + 2.5% Benzoyl Peroxide + 5% Ethyl Lactate (Score FORMULA 4)</th>
</tr>
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<tbody>
<tr>
<td>2</td>
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<td>1.03</td>
<td>3.85</td>
<td>3.15</td>
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<td>4</td>
<td>10.1</td>
<td>1.06</td>
<td>3.91</td>
<td>2.98</td>
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<td>1.01</td>
<td>1.05</td>
<td>3.87</td>
<td>3.03</td>
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<td>1.00</td>
<td>1.08</td>
<td>2.93</td>
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<td>1.01</td>
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Formula 2 versus Formula 1 = not significant  
(Calculated on mean × 2 weeks)
Formula 3 versus Formula 1 = $p < 0.01$  
(Calculated on mean × 2 weeks)
Formula 4 versus Formula 1 = $p < 0.01$  
(Calculated on mean × 2 weeks)
Formula 4 versus Formula 3 = not significant  
(Calculated on mean × 2 weeks)
Figure 1

Figure 2
Evident Erythema accompanied by desquamation

Intense Erythema without desquamation

Slight Erythema without desquamation

Barely visible Erythema

No Erythema

The results are shown in Tables I-III and Figures 5-8.

Calculation of colonies of Propionibacterium acnes

The calculation of Propionibacterium Acnes was carried out according to the method of Williamson and Kligman (14). Before taking the sample, both cheeks of the subjects (10 out of 20) were cleaned by using a sterile gauze saturated with a 0.1% sterile solution of Triton X-100, fol-

Figure 5
allowed by a further cleaning with distilled water and finally rubbed with a gauze saturated with hexane for 30 seconds. The cleansed skin was protected with a porous sterile plastic gauze, so as to maintain normal evaporative activity. After one hour a cylinder of sterile glass (internal area 3.8 cm²) with hollow base was applied to the area. Into said cylinder 1 ml of a sterile solution of 0.1% Triton X-100 in a pH 7.9 phosphate buffer was introduced. After having cleaned the area with a teflon spatula for one minute, two successive samples of liquid were taken. The samples thus obtained were diluted a number of times with a solution of 0.05% Triton X-100, immediately set in culture with a solution of 0.1% Tween 80 and incubated anaerobically for 7 days. The colonies of Propionibacterium Acnes were determined using the method of McGinley et. al. (15). The results obtained are shown in Table V and Figure 9.

**Determination of free fatty acids/triglycerides**

The ratio FFA/TG (Free fatty acids/triglycerides) was determined using the Downing method (16). One hour after having cleansed the area, according to the Williamson and Kligman method (14), the hollow-based glass cylinder was applied to the cheeks of the subjects (10 out of 20).
Into the above cylinder 2 ml of hexane were introduced, containing an internal standard of methyl nervonate. After cleansing the area with a small teflon spatula for 30 seconds, the hexane solution was filtered through a millipore filter (pore size 0.45 mm), in order to remove all the cellular debris and the bacteria, and dried under vacuum at 40°C. A TLC was then carried out to determine fatty acids and triglycerides. The results obtained are shown in Table V and Figure 10.

Results and comments
As can be seen from Tables I-III and figures 5-8, the new vehicle alone develops a considerable antiseborrheic activity, since it reduces the sebum level by around 10% (p<0.05) after two weeks of therapy, arriving gradually at reductions of 40% (p<0.01) after three months of continuous use. The sebosolving activity of this special anhydrous vehicle is further confirmed by the fact that the Tables I-III and figures 1-3 also show a total reduction of the number of comedones by about 18% (p<0.05) after three months use.

By controlling the activity of 5% Ethyl Lactate, of 2.5% Benzoyl Peroxide and of the mixture of both, it is evident that comedones and microcysts are reduced by 22% (p<0.05) and by 35% (p<0.01) after a treatment of only two weeks with 2.5% Benzoyl Peroxide and with the mixture of...
2.5% Benzoyl Peroxide and 5% Ethyl Lactate respectively.
On the contrary, the above lesions remain unchanged after two weeks of therapy with 5% Ethyl Lactate.
The average number of comedones and microcysts is strongly reduced even in the case of Ethyl Lactate alone, if the period of therapy is longer. In fact, after one month of therapy a reduction of about 13% (p<0.05) is reached, increasing to 30% after two months (p<0.01) and to about 60% after four months (p<0.01). As regards the reduction of the number of pustules and nodules, Ethyl Lactate starts to act only after one and a half month of therapy (reduction by 10% p<0.05). After three months, the gradual reduction is not greater than about 30% of the starting values (p<0.01).
Using Benzoyl Peroxide or, even better, the mixture of Benzoyl Peroxide and Ethyl Lactate, a reduction of nodules and pustules of 30% is obtained after the first month of therapy (p<0.05), reaching 70% (p<0.01) and 80% (<0.01) respectively after three months of therapy.
The values reported in Table IV and Figure 4, indicate the irritative and keratolytic activity of both Benzoyl Peroxide and the mixture Ethyl Lactate/Benzoyl Peroxide (p<0.01). The vehicle alone, and the Ethyl Lactate have proved themselves to be completely free of irritative effect, even after three months of use.
Table V and Figure 9 evidence the strong bactericidal activity of both Benzoyl Peroxide and the mixture Benzoyl Peroxi-
Ethyl Lactate, against the Propionibacterium acnes. These organisms are considerably reduced after only two weeks use of the products. The Ethyl Lactate alone shows only a bacteriostatic activity, whereas, combined, it appears to be capable of strengthening the effect of the Benzoyl Peroxide.

The ration FFA/TG shows (Table V and Figure 10) a reduction by about 50% of free fatty acids from the activity of both Ethyl Lactate and Benzoyl Peroxide, and from the mixture thereof (p < 0.01). It is known that Ethyl Lactate directly inhibits bacterial esterases, thus limiting the hydrolysis of triglycerides. Benzoyl Peroxide acts directly on the bacterial strains, thus reducing the production of esterase from Propionibacterium themselves.

From the foregoing, it plainly follows that it is possible to use Ethyl Lactate effectively in acne therapy, thus avoiding the irritative or photosensitizing effect of Benzoyl Peroxide. This is especially important in treating acne in fair skinned individuals.

Furthermore, Ethyl Lactate, in combination with a suitable vehicle, appears to be capable of enhancing the activity of Benzoyl Peroxide, thereby allowing the use of a lower concentration.

Finally, the exceptionally interesting activity of this new anhydrous vehicle, consisting of a special lipidic mixture with high volatility, is evident. This vehicle appears able to strongly reduce the surface lipidic film while facilitating penetration of both Ethyl Lactate and Benzoyl Peroxide through the pilosebaceous ducts.
REFERENCES

8. Belknap B.S. (1979) «Treatment of acne with 5 percent benzoyl peroxide gel or 0.05 percent of retinoic acid cream» Cutis 23, 856.
11. Mills O.H.D., Kligman A., Pochi P., Comite H. «Comparing 2.5%, 5% and 10% benzoyl peroxide on inflammatory acne vulgaris».