The topical application of clofibrate in the treatment of acne vulgaris

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ABSTRACT

Acne vulgaris is a common skin disease. The therapeutic approach to this disease includes standard topical and systemic agents to newly introduced alternative medications. This study suggests a new indication for clofibrate (the lipid lowering agent) & that is to be used topically in the treatment of acne vulgaris. The proposed mechanism is by decreasing lipid biosynthesis which takes place in the sebaceous gland. A total of 60 patients with visible papules and pustules of severe acne were enrolled in this study. Their age range between 13 – 31 years (24 males & 36 females). Healthy age matched controls (30 subjects) without any skin diseases were also participated in this study. Clinical investigations involved disappearance of signs and symptoms of the disease while the biochemical investigations involved measuring total cholesterol, HDL, LDL, & TG levels, SGOT, SGPT in the sera of all volunteers done before and 10 days after the topical application of clofibrate (500mg once daily).

The effectiveness of the topical application of clofibrate was approved in the treatment of acne vulgaris as a new clinical application of this drug and a novel strategy for the treatment of the disease as there was significant improvement 75% of the patients & moderate improvement for the rest of the patients.

In comparison with controls, patients with acne had higher total serum cholesterol and LDL levels with no significant difference in TG, HDL & enzyme levels.

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However, after the topical application of clofibrate, total serum cholesterol and LDL levels were decreased while no significant changes observed in the TG, HDL, GOPT, GPT serum levels. The results revealed that circulating lipid were slightly higher in patients with acne than control subjects but declined after treatment. Healing was accompanied with improvement in the symptoms of the disease. This might suggest that the lipid profile is one of the contributing or aggravating factors for this disease.

INTRODUCTION:

Acne vulgaris is the most common skin disease that primarily affecting adolescent, it is a chronic inflammatory disease of the pilosebaceous unit. The disease is self limiting but some people may still need treatment until their thirties or even fourties. Lesions are almost exclusively limited to greasy areas of the skin, including the face, ears, neck, upper back, and upper arms. Sebum is a lipid rich secretion of the sebaceous glands and has a central role in the pathogenesis of acne, since it provides a good growth medium for Propionibacterium acnes. Also the severity of the disease is generally proportional to the rate of sebum production. Increase in the secretion of sebum is stimulated by androgens at the time of puberty. Emotional stress, genetic factor, cosmetics, sweating, all have significant role in acne eruptions. Besides, Pre-existing acne may be erupted or even worsened by certain drugs like; phenytion, disulfiram, iodides, androgens, ACTH, thiourea, thiouracil, isoniazid … etc. Successful management of acne requires careful patient evaluation followed by consideration of several patient and medication factors when selecting a particular therapeutic regimen. The choice between topical and systemic therapy usually depends on the extent of skin involvement and severity of the disease. Topical drugs include tretinoin, benzoyl peroxide and some antibiotics. While systemic antibiotics are the mainstay of therapy in severe types of acne. Tetracycline, erythromycin, minocycline, doxycycline, clindamycin and trimethoprim/sulfamethoxazole are the most commonly used. This is accompanied by certain disadvantages such as most patients with antibiotic therapy require prolonged courses or frequent intermittent courses of therapy before significant remission occurs which might give chance for the drug to exert their side effects. Lack of improvement due to emergence of bacterial resistance is another problem which results in failure of therapy. The aim of this study is to introduce a new route of administration and indication for clofibrate. Clofibrate is a lipid lowering drug. It is usually used orally in a dose of 500mg to be given three times per day as an antihyperlipidemic agent. It lowers serum cholesterol and triglyceride (TG) levels by decreasing the VLDL and LDL while increasing HDL concentration in blood. The mechanism of action is not fully understood. But it stimulate lipoprotein lipase activity, hence increasing hydrolysis of TG.

In this work, clofibrate was tried to be applied topically on acne spots in a way to see whether it is going to cause any inhibition of lipogenesis in the sebaceous glands (by decreasing the lipid enrich sebum synthesis locally).

SUBJECTS AND METHODS:

A total of 90 subjects were enrolled in the study. Sixty patients with acute acne flare of age range 13 – 31 years (24 males and 36 females). Patients were diagnosed & followed up by a specialist dermatologist. The rest of the volunteers were 30 healthy age and sex matched controls. All participants were questioned for; timing of the disease, life style, exposure to chemicals or irritants, current drug therapy, dietary habits and family history of the disease.
Pregnants, nursing mother, smokers, patients with a history of chronic disease or other medications, all were excluded from the study. Clinical and laboratory evaluations were performed at the time of enrollment (day 0) and at the end of treatment (day 10).

Clinical assessment:
Patients were examined and diagnosed by a specialist dermatologist, the numbers of lesions were counted and deep nodules were detected. The severity of the disease was determined according to Burton et al. grading scheme\(^4\). Patients with grade 2, 3, 4, and 5 (mild–extremely severe) were included in the study.

Topical application of clofibrate:
Clofibrate content of one capsule (500mg) was aspirated from the soft gelatin capsule using a fine needle syringe and was applied topically once daily in a thin uniform layer on the affected area for ten consecutive days. Patients were asked to quit dietary intake of fat during the course of treatment.

Blood samples:
A blood sample (10ml) was withdrawn from each subject (after 12 hr. fasting) before treatment and 10 days after treatment. Each sample was left at room temperature for complete clotting. Serum was aspirated after centrifugation at 1000 rpm for 10 min. Total serum cholesterol\(^{22}\), HDL\(^{23}\), LDL\(^{24}\), TG\(^{25}\), aspartate aminotransferase (GOT)\(^{26}\) and alanine aminotransferase GPT\(^{26}\), were determined before and after clofibrate application.

Statistical analysis:
Data are expressed as mean ± SD, the student's t-test was used for statistical evaluation of significant difference between the two groups. (p<0.05 was considered a significant difference).

RESULTS:
Treatment Efficacy:
Clofibrate had been shown to be of high effectiveness and the severity of acne decreased dramatically within the first few days after initiation therapy. The drug was easily used and well tolerated by patients. There was significant improvement in 45 patients (75%), twelve patients (20%) showed mild to moderate response, 5% patients showed no improvement (this corresponds to 3 patients, 2 of them showed no improvement & the other patient discontinued treatment). Relapse occurred in 21 subjects, 2-4 weeks after cessation of therapy.

Adverse effects were mild and were (Fig-1)
1- Sweet taste sensation in 50% of patients.
2- Dryness in the applied lesion of the skin in 15% of patients.
3- Skin rash in 8% of patients.
FIG 1. SIDE EFFECTS OBSERVED AFTER TOPICAL CLOFIBRATE THERAPY

Biochemical analysis:
Serum triglyceride:
Triglyceride level was not significantly different between the patients and controls (table-1) also the triglyceride level, after treatment, was not significantly different from pretreatment or control levels.

Table 1. Serum triglyceride (mg/100ml) in acne vulgaris and control subjects.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=30)</th>
<th>Pretreatment (day 0) (n=60)</th>
<th>After treatment (day 10) (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG (mg/100ml)</td>
<td>65.76±10.51</td>
<td>69.41±12.98</td>
<td>68.88±11.84</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD
n=number of subjects

Total serum cholesterol:
The total serum cholesterol concentration was significantly higher in acne group in comparison with the control before treatment, the increase was estimated by 18% (table-2)

Table 2. Serum cholesterol levels in acne vulgaris and control subjects.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=30)</th>
<th>Pretreatment (day 0) (n=60)</th>
<th>After treatment (day 10) (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mg/100ml)</td>
<td>158.5±22.75</td>
<td>186.16±37.16</td>
<td>161.01±58</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD
n=number of subjects
* significantly different from control (p<0.05)
# significantly different from pretreatment level (p<0.05)
LDL – Cholesterol concentration:
The LDL level was significantly higher in the acne group in comparison with the controls before treatment. After 10 days of therapy (after healing) the level of LDL was significantly declined approaching the value of normal subjects (table-3).

Table 3 . S-LDL-Cholesterol level in acne vulgaris and control subjects.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=30)</th>
<th>Before treatment (n=60)</th>
<th>After treatment (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-Cholesterol (mg/100ml)</td>
<td>92.91±20.7</td>
<td>125.86±31.41 *</td>
<td>100.29±25.85 #</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD
n=number of subjects
* significantly different from control (p<0.05)
# significantly different from pretreatment level (p<0.05)

HDL – Cholesterol concentration:
Table – 4 shows that patients had lower means of HDL than normal healthy controls. After treatment, however, the level was not different from the pretreatment but significantly different from normal subjects.

Table 4 . Serum HDL-Cholesterol (mg/100ml) in acne vulgaris and control subjects.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=30)</th>
<th>Pretreatment (day 0) (n=60)</th>
<th>After treatment (day 10) (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-Cholesterol (mg/100ml)</td>
<td>52.43±12.77</td>
<td>46.42±.935 *</td>
<td>46.95±10.01 *</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD
n=number of subjects
* significantly different from control (p<0.05)

SGOT and SGPT:
No significant differences were found in the levels of SGOT and SGPT in all subjects (table–5).

Table 5 . SGOT and SGPT levels in acne vulgaris and control subjects.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=30)</th>
<th>Pretreatment (day 0) (n=60)</th>
<th>After treatment (day 10) (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGOT (IU/L)</td>
<td>12.23±3.2</td>
<td>11.12±4.2</td>
<td>10.9±6.15</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>16.15±1.2</td>
<td>15.96±3.41</td>
<td>14.31±45.12</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD
n=number of subjects
DISCUSSION:

Serum is a lipid rich secretion of the sebaceous glands and has a central role in the pathogenesis of acne, since it provides a good growth medium for P. acnes\(^{(3)}\). The severity of the disease is generally proportional to the rate of sebum production\(^{(15)}\), which is composed mostly of triglycerides (57%), wax esters (26%), squalene (12%), cholesterol esters (3%) and cholesterol (1.5%)\(^{(12)}\).

The pathogenic microorganisms most often found produce lipolytic enzymes releasing free fatty acids which have the ability to provoke a non specific type of inflammatory response\(^{(27,28)}\).

Clofibrate is a lipid regulating agent given orally, the mechanism of systemic effect has not been established definitely. The drug was found to potentate the action of lipoprotein lipase and interrupts cholesterol biosynthesis\(^{(20)}\).

In this work, clofibrate is introduced for the first time to be used topically in the treatment of acne. The drug was found very potent and highly effective, caused a marked reduction in sebum excretion, decreased the number of inflammatory papules and pustules in grade 2, 3, 4 and 5 acne patients.

Healing was achieved in only 10 days. The topical application of the drug on a limited surface area (restricted to the areas of acne only) for such a short period of time, excluded the possibility of side effects which might exert when the drug is taken orally and for a long period of time as an antihyperlipidemic agent. Reported systemic side effects were suspicion of causing malignant neoplasms, cholelithiasis, and pancreatitis besides other mild symptoms such as nausea, diarrhea, abdominal pain and myositis\(^{(29)}\).

None of the patients complained of any of the previously mentioned side effects. However, the only complaints were of unpleasant taste in 50% of patients, and very few complained of skin dryness and skin rash.

Thus the lowering level of the circulating lipids might be attributed to dietary factors rather than systemic effect since the amount of the drug applied (500 mg/day) and duration of application (10 days) on a very limited surface area (acne spots only) for all these a very low absorption, if any, would not be expected to produce any systemic effect.

Several other evidences stand against the postulation of a systemic effect of the drug, among these are the activity of SGOT and SGPT which were not changed after treatment as the two enzymes usually are elevated with oral clofibrate.

The TG level was not significantly changed and levels were within the normal range. Also, the lack of any of the side effects associated with systemic therapy is another evidence against the involvement of systemic effects of the drug.

Finally, the rapid onset of action in a relatively very short duration of time introduce clofibrate as a possible convenient anti-acne therapy alone or as a starting strategy for alleviating severe cases towards improvement stage.

Currently used anti-acne therapies are diverse and require frequent administration, many patients receive variety of topical and oral therapies with little improvement. Besides, conventional therapies might be associated with uncomfortable side effects as mild primary dermatitis, while systemic drugs are usually associated with gastrointestinal side effects.

In addition to super infection like candidiasis due to the long term use of antibiotics\(^{(28)}\). Others might lead to tissue pigmentation and liver diseases\(^{(30)}\).

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