The topical application of clofibrate in the treatment of acne vulgaris

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Received 10/5/2005 ; accepted 10/6/2005

الخلاصة

يعتبر حب الشباب من أكثر الأمراض الجلدية شيوعاً ويعالج بتناول الأدوية موضعياً أو فموياً أو كليهما .
تقدم هذه الدراسة استعمالاً طبياً جديداً لعقار الكلوفايبريت في علاج مرض حب الشباب , ولأول مرة أيضاً يتم استعماله موضعياً (وليس فموياً وكما هو معتاد في تخفيض مستوى الدهونات في الدم).
تم شمل 60 مريضاً مصابين بحالات متوسطة إلى حادة من مرض حب الشباب تتراوح أعمارهم من 13-31 سنة . (24 مريضاً من الذكور ويشكلون نسبة 40% و 36 من الإناث). إضافة إلى انضمام 30 شخصاً مصحاً وخالياً من الأمراض الجلدية والعضوية كمجموعة سيطرة وبعمرمقارب وعدد متساو من كلا الجنسين.
التحاليل السريرية شملت قياس الكولسترول , الدهن البروتيني العالي الكثافة (HDL) , الدهن البروتيني واطئ الكثافة (LDL) والكولسترول الثلاثي (TG) في مصل الدم وكذلك تم التحقق من تركيز أنزيمي SGOT,SGPT. اخذت عينات الدم للقيام بهذه التحاليل قبل البدء بالعلاج وبعد ذلك بعشرة أيام (بعد انتهاء العلاج) تم خلالها الاستخدام الموضعي للعقار يومياً ولمرة واحدة باليوم .
أكدت هذه الدراسة على فعالية عقار الكلوفايبريت باستعماله موضعياً لعلاج مرض حب الشباب . وقد كان هناك تحسن كبير جداً (شفاء) في75% من المرضى وتحسن بسيط إلى متوسط في الباقين .
أما التحليلات المختبرية فقد أوضحت بأن كلاً من الكولسترول, و LDL كانت في مستويات عالية عند مرضى حب الشباب بالمقارنة مع مجموعة السيطرة ولم يكن هنالك اختلاف ذا مغزى بين المجموعتين في مستويات SGOT,SGPT,HDL,TG.
أما بعد العلاج فقد حدث انخفاض كبير في تركيز الكولسترول , والـ LDL ولم يحدث أي تغيير ذو مغزى لمستويات TG, HDL ,SGOT,SGPT. انخفاض مستويات الكولسترول و LDL المصاحب لتحسن حالة المرضى * يؤدي إلى إقتراح ميكانيكية لعمل الكلوفايبريت وهو خفض تركيز هذه الدهون (أحد العوامل المسببة والمهيجة للمرض) موضعياً في الغدد الدهنية للجلد .

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 is 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[(1)]. Lesions are almost exclusively limited to greasy areas of the skin, including the face, ears, neck, upper back, and upper arms[(2)].
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[(3)]. Also the severity of the disease is generally proportional to the rate of sebum production[(4)].
Increase in the secretion of sebum is stimulated by androgens at the time of puberty[(5)]. Emotional stress[(6)], genetic factor[(7)], cosmetics[(8)], sweating[(9)], 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[(10)].
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[(11)]. Topical drugs include tretinoin[(12)], benzoyl peroxide[(13)] and some antibiotics[(14)]. 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[(15,16)]. 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[(17,18,19)].
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[(20)]. The mechanism of action is not fully understood[(21)]. 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 showns 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.

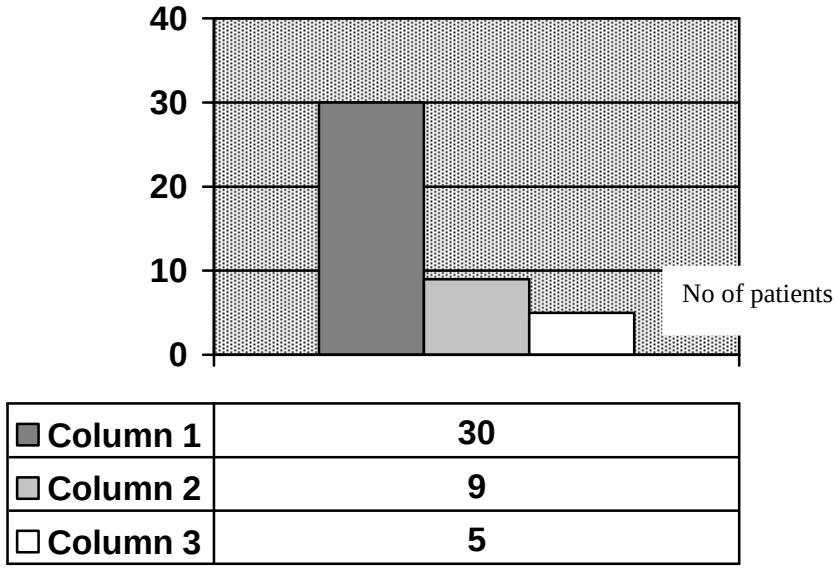

FIG 1 . SIDE EFFECTS OBSERVED AFTER TOPICAL CLOFIBRATE THERAPY

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.

	Control	Pretreatment (day 0)	After treatment (day 10)
	(n=30)	(n=60)	(n=60)
TG (mg/100ml)	65.76±10.51	69.41±12.98	68.88±11.84

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.

	Control	Pretreatment (day 0)	After treatment (day 10)
	(n=30)	(n=60)	(n=60)
Cholesterol (mg/100ml)	158.5±22.75	186.16±37.16 *	161.01±58 #

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.

	Control	Before treatment	After treatment
	(n=30)	(n=60)	(n=60)
LDL-Cholesterol (mg/100ml)	92.91±20.7	125.86±31.41 *	100.29±25.85 #

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.

	Control	Pretreatment (day 0)	After treatment (day 10)
	(n=30)	(n=60)	(n=60)
HDL-Cholesterol (mg/100ml)	52.43±12.77	46.42± .935 *	46.95±10.01 *

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.

	Control	Pretreatment (day 0)	After treatment (day 10)
	(n=30)	(n=60)	(n=60)
SGOT (IU/L)	12.23±3.2	11.12±4.2	10.9±6.15
SGPT (IU/L)	16.15±1.2	15.96±3.41	14.31±45.12

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%), squalere (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].

Non 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 drynem 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].

REFERENCES:

1- Kingman AM. Posta dole scent acne in women. Cutis. 1991, 48, 75.
2- Gupita MA, Johnson AM, Gupita AK. The development of an acne quality of life scale reliability, validity and relation to subjective acne severity in mild to moderate acne vulgaris. Acta. Dram. Venerol. 1998, 78, 451.
3- Level L, Marks R. Current views on the actiology, pathogenesis and treatment of acne vulgaris. Drugs, 1990, 39, 681.

4- Buton JL, Cunliffe WJ. The prevalence of acne vulgaris in adolescence. Br J Dermatol. 1971, 85, 119.
5- Pochi PE, Strauss JS, Downing DT. Age related changes in sebaceous glands activity. J. Invest Dermatol, 1979, 73, 108.
6- Mclntoch LJ, Hong KE, Sapolsky RM. Glucocorticoids may alter antioxidant enzyme capacity in the brain: baseline studies. Brain Res. 1998, 791, 209.
7- Goulden V, Mc Geown CH, Cunliffe WJ. The familial risk of adult acne: a comparison between first–degree relatives of affected and unaffected individuals. Br. J Dermatol. 1999, 141, 297.
8- Orentreich N, Durr NP. The natural evolution of comedones into inflammatory papules and pastules. J. Invest Dermatol. 1974, 62, 316.
9- Williams M., Cunliffe WJ, Gould D. Pilosebaceous duct physiology: effect of hydration on pilosebaceous duct orifice. Br. J. Dermatol. 1974, 90, 631.
10- Guldager H. Halothane allergy as cause of acne. Lancet. 1987, 1, 1211.
11- Thiboutot D. New treatments and therapeutic strategies for acne. Arch. Fam Med. 2000, 9, 179.
12- Alfonso R Gennaro. Remington's pharmaceutical science. 17th. ed., Pennsylvania, Mack Publishing company. 1985, 1567 and 863.
13- Bojar RA , Cunliffe WJ., Holland KT. The short–term treatment of acne vulgaris with benzoyl peroxide: effects on the surface and follicular cutaneous microflor. Br. J. Dermatol. 1995, 132, 204.
14- Stoughton RB. Topical antibiotics for acne vulgaris. Arch. Dermatol. 1979, 115, 486.
15- Marples RR, Kligman AM. Ecological effects of oral antibiotics on the microflora of human skin. Arch. Dermatol. 1971, 103, 148.
16- Leyden JJ. Absorption of minocycline hydrochloride and tetracycline hydrochloride effect of food, milk, and iron. J. AM. Acad. Dermatol. 1985, 12, 308.
17- Poulos ET, Tedesco FJ. Acne vulgaris: double blind trial comparing tetracycline and clindamycin. Arch Dermatol. 1976, 112, 974.
18- Leyden JJ. Retinoids and acne. J. AM. Acad. Dermatol. 1983, 19, 164.
19- Cunliffe WJ, Aldano OL, Goulden V. Oral trimethoprim: a relatively safe and successful third line treatment for acne vulgaris. Br. J Deratol. 1999, 141, 757.
20- Kathleen Parfitt. Martindale. The complete drug reference. 32 nd. ed. The Pharmaceutical press. 1999, vol. 2, 1271.
21- Rang HP, Dale MM, Ritter JM. Pharmacology. 4 th, ed., Churchill Livingstone. 2000, 307.
22- Richmond W. Clinical chemistry. 1973, 19, 1350.
23- Jacobs NJ, Vandenmark PJ. Arch Biochem. Biophys. 1960, 88, 250.
24- Friedwald WT, Levy RI, Fredrickson DS. Estimation of the concentration of LDL–Cholesterol in plasma without the use of the preparative ultracentrifuge. Clin. Chem. 1972, 18, 499.
25- Fossati P., Principe L. Serum triglyceride determined colorimetrically with an enzyme that produce hydrogen peroxide. Clin. Chem. 1982, 28, 2077.
26- Reitman S. and Frankel S. As cited by Randox kit (UK). Am J Clin Path. 1957, 28, 56.
27- Rook/Wilkinson/Ebling. Textbook of Dermatology. Vol. 3, Oxford, Blackwell Science Ltd. 1998, 1927.
28- Vowels BR, Yang S, Leyden JJ. Induction of proinflammatory cytokines by soluble factor of propioribacterium acnes: implication for chronic inflammatory acne. Infect Immun. 1995, 63, 3158.
29- Weingarten CT. Nurse's drug guide. 4th. ed. Springhouse. 2002, 362.
30- Hoefangel JJ, Van–Leeuwen RL, Mattie H, Bastiaens MT. Side effects of minocycline in the treatment of acne vulgaris. Ned. Tijdshr. Geneeskd. 1997, 141, 1424.