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A NEW PRINCIPLE FOR THE TREATMENT OF ACNE

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Abstract. On the assumption that an increased sebum production and a liberation of fatty acids by bacterial esterases are important stages in the pathogenesis of acne, ethyl lactate dissolved in ethyl alcohol has been investigated as to its usefulness as therapeutic agent against acne. It was found that ethyl lactate is stabile in ethyl alcohol, hydrolyses slowly in water and rapidly in serum. Pig liver esterases increase the hydrolysis rate of ethyl lactate. As ethyl lactate is lipid soluble, it is assumed to penetrate into the sebaceous ducts. After a few hours, ethyl lactate, by being hydrolysed, brings down the pH of serum-like tissue fluid to between 4 and 5, when ethyl lactate is added in the amount of about 0.7%. This lowering of the pH inhibits the bacterial esterases. The clinical effect on acne of using ethyl lactate solution applied with a cotton pellet it obvious, though very good when used as an occlusive dressing applied for 3 minutes to skin surface affected by acne lesions.

The pathogenesis of acne is not fully known. One important factor seems to be an increased sebum production. The average acne patient has a higher sebum excretion rate than non-acne individuals of corresponding age (4, 9, 10). One of the clinical features of acne is seborrhoea; another is the presence of comedones.

Pure sebum is estimated to contain about 57.5% triglycerides, 26% wax esters, 12% squalene, 3% cholesterol esters, and 1.5% free cholesterol, thus free fatty acids are absent (5). The surface of the human skin and the pilosebaceous duct contain unspecific esterases (8, 13). These enzymes are probably responsible for the relatively high content of free fatty acids of the surface lipids of the skin.

In acne vulgaris patients there does not seem to be a significant increase in the free fatty acid content of sebum (9, 10). The ratio of free fatty acids to triglycerides, however, is increased (10). When treating acne with tetracyclines, the free fatty acid content of sebum decreases (3). Free fatty acids of a chain length of 8 to 14 carbon atoms are particularly irritating when applied to the skin (6). Intradermal injection of sebum produces an inflammatory reaction (14).

It is generally believed that a liberation of free fatty acids in the pilosebaceous duct by esterases is an important step in the pathogenesis of acne vulgaris. Although not definitely proven, it seems likely that microorganisms such as corynebacterium acne and coagulase-negative staphylococci contribute with esterase activity in the pilosebaceous apparatus (1, 7, 11, 12, 13). The esterases of corynebacterium acne and coagulase-negative staphylococci have a pH optimum around 7 and the activity decreases appreciably below pH 6 (2).

Although our knowledge of the pathogenesis of acne vulgaris is incomplete and uncertain it may suggest a few simple therapeutic possibilities that hitherto have not been explored systematically.

The increased sebum secretion rate in acne, together with the theory that sebum is the substrate of enzymes liberating acnegenic free fatty acids, suggest that an extraction of lipids once or several times daily may be helpful in the treatment of acne. The best solvent in this respect may be ethanol with the addition of glycerol or propylene glycol to counteract the drying effect.

The sensitivity of the bacterial lipases to low pH suggests than one should try to decrease the pH of sebaceous ducts. This may be achieved by an acid or an easily hydrolysable ester, which gives rise to a non-toxic and non-acnegenic acid. The ester may have a better penetration capacity into the sebum as it is probably more lipid soluble. Ethyl lactate seems to be a suitable ester for this purpose. It gives rise to lactic acid and ethyl alcohol after hydrolysis.

In the present paper some relevant properties of

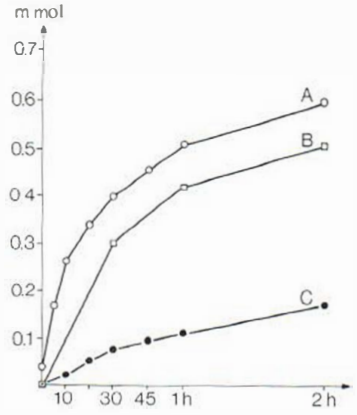

Fig. 1. The number of mmoles lactic acid liberated after different intervals when 100 μl ethyl lactate is added to 10 ml serum. Curve A with further addition of 3 IU esterase, curve B with the addition of 1 IU esterase, and curve C without addition of esterase.

ethyl lactate are reported, together with the results of the clinical effect of ethyl lactate solution on acne.

MATERIAL AND METHODS

Laboratory study

Standard curves were made with pH as a function of mmoles of lactic acid added to 0.9% NaCl solution and serum respectively. Ethyl lactate was then added to the solution or serum and the pH was measured after various incubation periods at 30°C. The count of mmoles of lactic acid liberated was then determined with the help of the standard curves. In some experiments pig liver esterase (purchased from Boehringer Mannheim GmbH) was added to the solution. The amount of esterase added was expressed as IU (1 IU equals approximately 0.01 mg of the enzyme preparation).

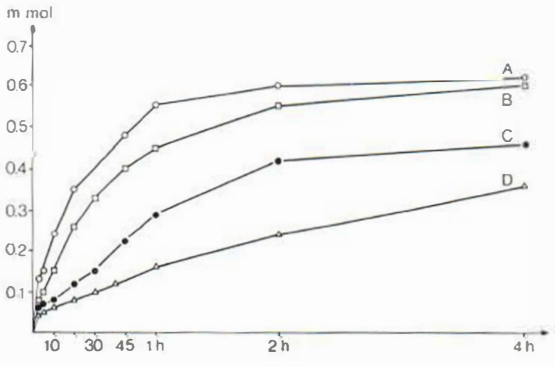

Fig. 2. The effect of ethyl alcohol on the hydrolysis of 1% ethyl lactate in 10 ml serum with 3 IU esterase added. Curve A no ethyl alcohol added, curve B with 1% ethyl alcohol, curve C with 5% ethyl alcohol and curve D with 10% ethyl alcohol.

Clinical study

Patients attending the Department of Dermatology, Karolinska Hospital, for acne took part in this investigation. It was not considered possible to make a double-blind study in a strict sense because of the easily recognizable smell of the ethyl lactate and nature of the application of the preparation in the second part of the clinical experiment.

The preparation used contained: ethyl lactate 10, glycerol 5–10, and ethanol 80–85. Patent applications filed.

In the first experiment 10 patients with slight to moderate acne took part. These patients applied the solution with a cotton pellet twice a day to the skin areas where the acne lesions were located. The patients were examined 1 month later.

In the second experiment the patients put a soft paper cloth on aluminium foil and dropped the solution on the cloth until it appeared well soaked. They then applied this wet dressing to the skin area to be treated with the aluminium foil outermost. They then kept the dressing in position for 3 minutes. This was done twice daily. In this experiment 20 patients took part. The effect was expressed in the following way: + + = considerably better than before the treatment with not more than one superficial pustule appearing during the last 2 weeks, + = better than before the treatment but new lesions still appearing, and 0 = no significant difference. The patients were examined one month later.

Photographs were taken of most patients before the treatment to facilitate the evaluation of the effect. In the present study no attempt was made to classify the severity of the acne before the treatment.

RESULTS

Laboratory studies

Ethyl lactate 10% in ethanol stored at 40°C for 1 week shows no sign of decomposition, as established by pH measurements after diluting the solution with an equal quantity of water. In pure water or saline the ethyl lactate lowers the pH somewhat immediately but the decomposition of ethyl lactate into ethyl alcohol and lactic acid gives a further decrease in pH of the solution. If 1 ml ethyl lactate is added to 100 ml saline only about 1% of ethyl lactate is hydrolysed after 4 hours.

After adding ethyl lactate to serum a decrease in pH takes place rather rapidly. Fig. 1 shows the number of mmoles lactic acid liberated after various intervals when 100 μl ethyl lactate is added to 10 ml serum (curve C). By adding 1 IU (Fig. 1, curve B) and 3 IU (Fig. 1, curve A) the hydrolysis of ethyl lactate proceeds correspondingly faster. Serum itself has an esterase activity of less the 1 IU per 10 ml.

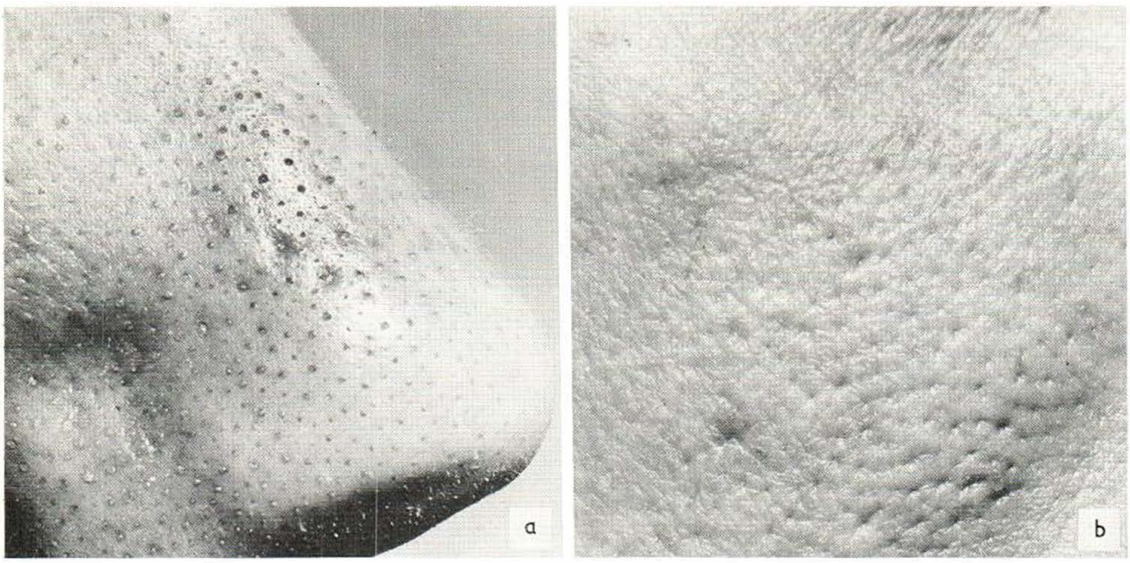

Fig. 3. (*a*) An untreated part of the face with conspicuous comedones and seborrhoea. (*b*) A part that has been treated with occlusive ethyl lactate dressing 3 min twice daily for 2 months. Small depressions after the comedones are seen. The skin is less seborrhoic.

Fig. 2 shows the effect of ethyl alcohol on the hydrolysis of ethyl lactate in serum with the addition of 3 IU esterase per 10 ml serum. One per cent ethyl alcohol gives a small, and 10% a significant retarding of the hydrolysis of ethyl lactate but about the same end result is obtained in all cases. On adding 1% glycerol or 1% propylene glycol, no significant effect is found on the release of lactic acid from 1% ethyl lactate in serum.

To obtain a pH lower than 6 it is necessary to add 0.4% ethyl lactate to serum and pH 5 is obtained by adding 0.7% ethyl lactate. These values are obtained within an hour if 10 ml serum contains 3 IU pig liver esterase.

Clinical studies

The general impression is that the treatment with ethyl lactate, whether applied with a cotton pellet or used as an occlusive dressing, causes no cosmetic problems as the solution does not stain and leaves no visible traces on the skin. Especially after the occlusive treatment, even those patients with the most pronounced seborrhoea were free from the oily appearance of the skin which is so common in acne patients. This effect lasts for at least 10–12 hours after each treatment with the occlusive dressing.

The comedones were less conspicuous or had disappeared after the treatment, as is illustrated in Fig. 3. The effect on acne lesions is given in Table I. The ethyl lactate solution used as an occlusive dressing is thus more effective than when applied with a cotton pellet.

Two of the patients who have used the occlusive treatment had a very severe acne and were on a small tetracycline (0.25 g × 2) dose for 6 weeks when the present treatment was started. No satisfactory effect of the tetracycline was noticed prior to the ethyl lactate treatment. Because of the severity of the acne in these two cases, the tetracycline medication was continued during the ethyl lactate treatment. The patients reacted very well during the combined tetracycline–ethyl lactate treatment.

DISCUSSION

The topical acne therapy used to-day is mainly based on practical experience. The theories of the role of bacterial esterases and free fatty acids in the pathogenesis of acne have been the basis for the therapeutical method described in the present paper. The mode of action of this method is thought to be two-fold. It is intended to give a good extraction of sebum from the skin surface

Table I. *Clinical effect of ethyl lactate solution on acne vulgaris*

Effect	Number of patients	
	Ethyl lactate	
	Applied with cotton pellet	Used in occlusive dressing
+ ÷	4	17
+	3	2
0	3	1

and sebaceous ducts and to inhibit lipase activity on these locations.

The clinical study has shown that even in the most seborrhoeic patients the skin has a matt appearance for about 12 hours after the occlusive dressing treatment before it becomes oily. Vigorous exercise and sweating may, however, reduce this interval. In contrast to many other preparations, this matt appearance is that of the skin surface itself and is not caused by any externally applied powder.

The second factor, the inhibition of lipase activity, is difficult to study directly on the skin of patients. The laboratory studies presented here show that ethyl lactate is stable in ethyl alcohol. It hydrolyses slowly in water and rapidly in serum. By adding pig liver esterase the hydrolysis proceeds still faster. This process slows down appreciably as the pH decreases, or if ethyl alcohol is added. This may be due to an inhibition of the esterase by low pH (cf. 2) and by ethyl alcohol. The latter may also act by deflecting the reaction ester + water $\rightleftarrows$ acid + alcohol to the left.

The final pH does not seem to be affected appreciably if ethyl lactate and ethyl alcohol are added in the proportion 1 to 10. The amount of ethyl lactate that has to be present in a tissue fluid with the same buffering capacity as serum to give a final pH of 6 is about 0.4%, and for a final pH of 5, about 0.7%. By using the occlusive dressing it seems reasonable to assume that these concentrations are obtained in the sebaceous ducts. The treatment time of 3 min with the occlusive dressing is more or less arbitrarily chosen. The effect may vary with length of treatment. In this paper the principles for the ethyl lactate treatment are presented, but more work is needed in order to find the optimum conditions for the use of ethyl lactate in the treatment of acne.

Ethyl lactate has two advantages over lactic acid in an acne preparation. It is much more lipid soluble and may thus penetrate better into the sebaceous ducts. Since the hydrolysis of ethyl lactate is inhibited between pH 5 och 4 there seems to be no risk of obtaining too low a pH. The "ethyl lactate-tissue fluid" system thus seems to be self-regulating with respect to pH, giving values just below 5, provided enough ethyl lactate is present.

The lactate seems to be the most physiological and harmless type of ester to use, as lactic acid is a compound which the body is used to handling. It may, however, be advantageous to use glycerol lactate although this ester is more difficult to obtain.

The acne therapy proposed in the present paper is thus based on the modern theories of the pathogenesis of acne. It has a good clinical effect and is rather simple to use. It does not stain and is cosmetically very favourable. It may also be used against seborrhoea and pityriasis oleosa capitis. The only drawback found as yet with this treatment is a strong "aromatic" smell which is felt during the treatment and a few minutes after.

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