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Hydrogen Peroxide Cream: An Alternative to Topical Antibiotics in the Treatment of Impetigo Contagiosa

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In total, 256 patients with bacteriologically verified impetigo contagiosa were included in three double-blind, parallel group, randomized, multi-centre trials, where the efficacy of hydrogen peroxide cream (Microcid®) was compared with that of fusidic acid cream/gel (Fucidin®). The trials were performed at 47 centres in three countries, Sweden, Germany and UK, and the results are compiled in the present report. During the course of the 3-week treatment period, 92 patients out of 128 (72%) in the Microcid® group were classified as healed, compared to 105 patients out of 128 (82%) in the Fucidin® group. This difference was not statistically significant. The reduction in composite sign severity score (the sum of the score for erythema, vesiculation/bullae, weeping and crusting divided by four) in each separate study was 73%, 78% and 84% in the Microcid® group and 85%, 85% and 84% in the Fucidin® group. No statistically significant differences were found in the separate studies or when compiling the studies in a meta-analysis. When the patients had been classified as healed, β-haemolytic streptococci were eliminated in all patients treated with Microcid® cream. Since treatment started before the result of the bacteriology was known, another 135 patients with negative skin culture were enrolled in the trials, i.e. 391 patients were included in the safety analysis. Out of these, 23 patients reported the occurrence of adverse events, mainly classified as mild. In conclusion, Microcid® cream has been documented as a topical alternative to fusidic acid in the treatment of impetigo. ***Key words: topical treatment; superficial skin infection; clinical trial; Staphylococcus aureus; β-haemolytic streptococci; bacteriological culture.***

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Impetigo contagiosa is a clinically well-defined and common superficial skin infection, mainly seen in children (1, 2). Impetigo is caused by *Staphylococcus aureus* and/or β-haemolytic streptococci. *S. aureus* is the dominating cause in temperate climates, whereas in humid and tropical areas β-haemolytic streptococci are more prevalent.

The most commonly used treatment for impetigo contagiosa is topically administered antibiotics. These compounds possess a bactericidal effect, resulting in healing of the lesions. However, one of the major drawbacks of topical antibiotics is the risk of developing bacterial resistance (3). This risk makes it desirable to have alternative products with a potent antibacterial effect.

Hydrogen peroxide solution has been used for many years in the clinic for treatment of skin and wound infections. Extensive in vitro studies document a good antibacterial effect against gram-positive as well as gram-negative bacteria (4). However, drawbacks with hydrogen peroxide are the short time of action, because of a high degradation rate, and local irritation.

A new cream formulation, Microcid®, stabilizes hydrogen peroxide, avoiding fast degradation, with the result that the antimicrobial effect is prolonged. This new formulation is based on crystalline lipids (5, 6). Three studies have been undertaken to compare the effect of Microcid® cream with that of a topical antibiotic commonly used in impetigo, fusidic acid (Fucidin®). The results from these studies have been compiled in the present report.

MATERIAL AND METHODS

In total, 391 patients (114 in Sweden, 121 in Germany and 156 in UK) were enrolled in three double-blind, parallel, randomized (in blocks of four), multi-centre trials involving 47 centres in the three countries (8 in Sweden, 10 in Germany and 29 in UK). In Sweden, the trial was performed in cooperation between specialists in dermatology and general medicine; in Germany only specialists in dermatology were involved and in UK the trial was performed by general practitioners. The same study protocol was used, but the three studies were performed independently of each other. All but 9 patients had impetigo localized to the face, and the patients were not allowed topical and systemic antibiotic treatment for 2 and 4 weeks, respectively, prior to start of the study. Only patients from 3 years of age were included. In the German study, an upper limit was set to 40 years of age. The individual study protocols were approved by each national medicine control authority and ethics committee, and informed consent was obtained from all patients before they were enrolled in the study.

After the patients had been enrolled, a swab for bacteriological culture was taken from the skin lesions, as well as from the throat. For ethical reasons, all patients started on the trial medication immediately. However, in the final efficacy analysis, only patients showing growth of either *S. aureus* or β-haemolytic streptococci, alone or in combination, in the skin lesions, were included. In total, 256 patients (131 men, 125 women; mean age 17.9 years in the Microcid® group and 16.6 years in the Fucidin® group, range 3–74 – one patient was 2 years old) were included in the final analysis of efficacy.

The patients were treated either with Microcid® cream 1% (hydrogen peroxide, Bioglan AB) or Fucidin® 2% (fusidic acid, Leo Pharmaceuticals). In Sweden and Germany a cream formulation of Fucidin® was used, whereas a gel formulation was used in the UK. The tubes were put into identical paper boxes, to keep the trials blind. One hundred and twenty-eight patients were treated with Microcid® cream (M-group) and 128 patients with Fucidin® (73 with the cream and 55 with the gel) (F-group). The treatment was performed 2–3 times daily for a maximum of 3 weeks. If the patient was classified as healed, the treatment was stopped earlier. The patients were instructed to wash the lesions properly with water and a mild soap before each application and to remove crusts.

The patients were assessed at start and after 3, 7, 14 and 21 days of treatment. The following signs and symptoms of erythema, vesiculation/bullae, weeping, crusting, scaling, soreness/burning and itching were recorded on a 0–4 scale, where 0 = none, 1 = very mild, 2 = mild, 3 = moderate and 4 = severe. A patient was defined as healed when all signs and symptoms were 0, except for erythema and scaling where score 1 was accepted. As another efficacy variable, the composite sign severity score (CSSS = the sum of erythema, vesiculation/bullae, weeping and crusting, divided by four) was used. During the study, all

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Table I. *Proportion of patients classified as healed and the composite sign severity score (CSSS) at start and at endpoint, for each separate study*

The results from the meta-analysis of the "odds ratio" (= risk ratio) for the proportion of healed patients and for the CSSS are presented as 95% confidence interval (CI). Endpoint = "last observation carried forward", i.e. the last recorded value for each patient independent of when the patient left the trial.

Study	Microcid® Healed		Fucidin® Healed		Microcid® CSSS start	Endpoint	Fucidin® CSSS start	Endpoint
Sweden	30/37	81%	35/39	90%	3.34	0.52	3.17	0.46
Germany	31/44	70%	26/34	76%	3.27	0.72	3.33	0.51
UK	31/47	66%	44/55	80%	2.83	0.76	2.85	0.45
Total	92/128	72%	105/128	82%				
	"Odds ratio" 95% CI				CSSS 95% CI			
Total	0.604–1.271 n.s.				−0.424–0.068 n.s.			

spontaneously reported adverse events, like stinging, burning, pruritus, were recorded.

Statistical analysis was carried out for each individual study by using Chi-square and Fisher's exact tests. The efficacy was also expressed as within patient deviations in the CSSS from start of treatment, where differences between the treatment groups were tested by means of the analysis of variance (ANOVA) two-tailed test. An overview has been performed, where data from all three studies have been analyzed in two different ways: either by adding up to a total, independent of trial (i.e. pooling), or by considering the variation from different studies, i.e. meta-analysis (7). In the overview, the frequency of healed patients has been analyzed with a 95% confidence interval (CI) for the odds ratio and for the CSSS, the standardized mean difference between the treatments has been analyzed with a 95% CI.

RESULTS

Of the 391 patients enrolled, 256 patients had a bacteriologically verified impetigo, 199 of whom (78%) showed growth of *S. aureus*, 21 (8%) of β-haemolytic streptococci, and 36 (14%) of both *S. aureus* and β-haemolytic streptococci. In total, 24 patients, 12 in each treatment group, were found to have growth of β-haemolytic streptococci in the throat. Only 10 of these patients were prescribed systemic antibiotics and thus withdrawn from the study.

The results of patients classified as healed are illustrated in Table I. In total, 92 patients of 128 in the M-group were classified as healed, compared to 105 patients of 128 in the F-group. This difference was not statistically significant, not even when using the meta-analysis approach. The mean (± standard error) duration of treatment was 14.4 ± 0.6 days in the M-group and 12.4 ± 0.6 days in the F-group.

As illustrated in Table I, the reduction in CSSS in each separate study is 73%, 78% and 84% in the M-group and 85%, 85% and 84% in the F-group. No statistically significant differences were found in the separate studies or in the meta-analysis.

When classified as healed, 24 patients (15 M-group, 9 F-group) showed growth of *S. aureus* on the skin and one patient (F-group) still showed growth of both *S. aureus* and β-haemolytic streptococci. The latter patient was the only one among 57 patients who still showed growth of streptococci at the end of the treatment. In the study performed in UK, 30 patients out of 31 healed in the M-group and 40 out of 44 healed in the F-group returned for a post-treatment follow-up. All patients but one patient treated with Fucidin® were without clinical signs of impetigo 7 days after the end of treatment.

Eleven patients (5.6%) in the M-group were withdrawn due to deterioration of their impetigo. The corresponding figure for the F-group was only 3 patients (1.5%). This difference was statistically significant ($p = 0.0318$). No patient treated with Microcid® was withdrawn due to adverse events, whereas 3 patients treated with Fucidin® gel were withdrawn. The reason for their withdrawal was irritation of skin, burning and blistering. Of all 391 enrolled patients, 23 patients (5.9%) reported the occurrence of some adverse event on one or more occasions during treatment, 14 treated with Microcid® and 9 treated with Fucidin®. In general, the adverse events were classified as mild.

DISCUSSION

In the present study, no significant difference in clinical efficacy between Microcid® cream and Fucidin®, either as cream or gel, was observed. The proportion of patients healed was in the same range as for other studies using topical treatment (8, 9). However, in each separate study, there was a tendency towards a somewhat lower clinical efficacy of Microcid® cream compared to Fucidin®. This is also emphasized by the fact that a few more patients in the M-group were withdrawn due to deterioration of impetigo.

The bacteriological results show that most of the bacteria are eliminated from the skin with topical treatment. However, when healed, about 10% of the patients showed growth of bacteria, mainly *S. aureus*. This finding is not surprising considering the fact that *S. aureus* colonizes the skin of an increasing number of healthy individuals and that no quantitative measurements of the bacteria have been performed in the present study. There was only one patient from the Fucidin® group with growth of β-haemolytic streptococci when classified as healed. This result corresponds well with the effect of Fucidin® on β-haemolytic streptococci, as described by Bojs (1). In no patient classified as

healed in the Microcid® group was growth of β-haemolytic streptococci observed. This indicates that Microcid® possesses a strong bactericidal effect on this multi-pathogenic strain of bacteria.

Development of bacterial resistance is an increasing problem in clinical medicine, and a wellknown phenomenon when using topical antibiotics (3). This is especially a problem when the same antibiotic is used both topically and systemically (10). Recently, a new antibiotic for topical use only, mupirocin, was introduced on the Swedish market. However, frequent use of this antibiotic has also given rise to resistant bacteria (10). Hydrogen peroxide does not give rise to resistant bacteria and therefore Microcid® cream seems to be a most valuable alternative in the treatment of superficial skin infections. Also, another favourable circumstance of the topical use of Microcid® is that no reports exist in the literature concerning the development of allergic contact dermatitis to hydrogen peroxide or other ingredients in Microcid® cream. This is not the case with fusidic acid and the antioxidant in the cream base (11, 12) or other topical antibiotics as neomycin and bacitracin (13, 14). Thus, also from this point of view, Microcid® cream seems to be an important product for topical treatment of superficial skin infections.

Both treatment with Microcid® and with Fucidin® was well tolerated, with only 6% of all enrolled patients reporting an adverse event. Despite the fact that the adverse events were reported as mild by most of the patients, 3 patients treated with Fucidin® gel had to be withdrawn due to burning and irritation of the skin.

In the present study, Microcid® cream is documented as an effective therapeutic topical alternative to commonly used formulations in the treatment of impetigo. Hydrogen peroxide is effective against both gram-positive and gram-negative bacteria and has now been stabilized in a cosmetically well accepted cream base. Probably, Microcid® cream is also effective in the treatment of other superficial skin infections than impetigo. The minimal risk of inducing bacterial resistance and/or allergic contact dermatitis also makes Microcid® cream a valuable alternative to products used topically at present.

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