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Erythromycin 3% & Benzoyl peroxide 5% Gel for Acne

Benzoyl peroxide 5% plus erythromycin 3% (Benzamycin[®] gel, Dermik) has been available in the USA since 1984, in the UK since 1995, and was approved in Canada recently. Benzoyl peroxide has been available since the 1960s and topical antibiotics have been used since the 1970s. Combinations of anti-acne medications have been utilized by practitioners searching for treatment that improves compliance, so it is hardly surprising that erythromycin and benzoyl peroxide are now available combined in a gel preparation.

Indications

Benzamycin[®] is indicated for the topical treatment of moderate acne vulgaris characterized by comedones, inflammatory papules/pustules with or without an occasional cyst or nodule. It is not indicated for cystic acne.

Clinical Studies

In double-blind studies, the combined preparation was significantly more effective against inflammatory lesions than erythromycin or benzoyl peroxide used alone.^{1,2}

Benzamycin[®] has been shown to be more effective than clindamycin phosphate solution³ and clindamycin phosphate lotion.⁴ There are no studies comparing Benzamycin[®] with benzoyl peroxide and erythromycin prescribed separately.

Bacterial Resistance

Use of topical preparations of antibiotics selects for antibiotic-resistant bacteria because of the gradient of drug concentration present at the periphery of the

treated area.⁶ Propionibacteria highly resistant to erythromycin⁵ are found on the skin of 25% of antibiotic-treated acne patients.⁶ Strains resistant to erythromycin usually exhibit some cross resistance to clindamycin. The combination of erythromycin and benzoyl peroxide is said to be safer because it does not promote the overgrowth of erythromycin-resistant coagulase-negative staphylococci that occurs when erythromycin is used alone.⁶ In a recently published study, the combination of 5% benzoyl peroxide and 3% erythromycin had greater *in vivo* antipropionibacterial activity than 3% erythromycin alone, and brought about significant clinical improvement in acne patients with high numbers of erythromycin-resistant propionibacterial strains pre-treatment.⁶

Side Effects

Benzoyl peroxide used alone is usually more irritating than topical antibiotics, causing erythema and scaling sometimes accompanied by transient burning and/or itching.⁷ However, in a cumulative irritation test, the combination product was significantly less irritating than benzoyl peroxide alone.⁸ The reduced irritancy has been attributed to the anti-inflammatory effect of the erythromycin. The Benzamycin[®] gel can cause some erythema, burning, and itching at first, but this usually subsides despite continued treatment.⁹ Affected patients can try using less gel or applying it only once daily until the irritation subsides. Moisturizers can be used to counteract any dryness or scaling.⁹ The benzoyl peroxide can bleach hair or coloured fabrics.

Safety During Pregnancy & Lactation

The safety of Benzamycin[®] in pregnant or breast-feeding patients is unknown but seems unlikely to be a problem, as even when administered systemically, erythromycin is

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not known to be harmful to pregnant patients and is only excreted in small amounts in breast-milk.

Administration

A thin layer of Benzamycin® should be applied to affected areas twice daily. Areas to be treated should first be washed thoroughly with a non-medicated soap, rinsed with warm water, and gently patted dry.

Clinical Assessment

Benzamycin® gel is a stable formulation of benzoyl peroxide 5% and erythromycin 3%, which is useful in the treatment of Acne vulgaris and has a low potential for producing resistant organisms. Although it is not known how effective it is compared with the two drugs prescribed separately, Benzamycin® is simpler to use and likely to improve patient compliance. It is not as irritating as benzoyl peroxide used alone. Daily costs of using Benzamycin® are similar to the cost of using other commonly prescribed anti-acne combinations. ☺

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Scalp Psoriasis

Psoriasis afflicts 1-3% of the general population^{1,2} and affects the scalp in about 40% of those suffering from the disease.³ In some patients, the scalp is the only site affected.⁴ In long-standing scalp psoriasis, hair thinning does occur.⁵ For the patient, scalp psoriasis is itchy and uncomfortable, and cosmetically disturbing because of shedding of scales. It is difficult to manage⁶ because treatment is unpleasant, generally produces indifferent results, only partial control and relapse rates are high.⁵ Patient compliance is often poor as currently available medications are often greasy, sticky, odorous, can cause changes in hair color, are difficult to apply, require frequent application, and are expensive.

Treatment

Psoriasis of the scalp is often a therapeutic challenge. Topical treatment is the favourite treatment approach – systemic treatment is not as effective.⁷ The vehicles for topical scalp preparations are usually clear gels or lotions suitable for easy application and subsequent removal by the patient.⁸

• Traditional Preparations of Coal Tar or Anthralin

Tar preparations are disagreeable to use, and both coal tar and anthralin preparations stain. Crude coal tar (2-5%), with 5-10% salicylic acid incorporated in petrolatum, is very messy, but can be useful for treating in-patients' recalcitrant psoriasis. Purified tar preparations are more suitable for treating out-patients. Note that some patients may require treatment each week for up to two months. Shampoos containing coal tar can be used by patients as frequently as necessary. Anthralin causes skin irritation and great care must be taken to avoid contact with the eyes.⁸

The carcinogenicity of coal tar has clearly been demonstrated by *in vitro* and animal studies, and appears to be potentiated by concomitant use of ultraviolet radiation. Systemic absorption of mutagens from topically applied tar has been demonstrated in humans. Conclusive evidence for the carcinogenicity of tar used in dermatologic practice is lacking,⁹ and will only be provided by cohort studies involving several thousand patients. Our lead article in the very first issue of this *Letter* was entitled, "Should coal tar preparations be widely available without prescription?"¹⁰

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Female Hair Loss

Androgenetic alopecia is a stressful experience for both sexes, but possibly more distressing for women. Relative to female controls, women with androgenetic alopecia have more social anxiety, poorer self-esteem and psycho-social well-being, less of a sense of control over their lives, and a less satisfying quality of life.¹

Female androgenetic alopecia is a common and perplexing clinical problem. Although there are no reliable data, Professor Constantin Orfanos of Berlin feels that 20-40% of European women have androgenetic hair loss to some extent.² Earliest onset is at puberty, while later onset occurs in the second to fourth decade of life. The most common pattern of hair loss is the diffuse parietal thinning of scalp hair with retention of the frontal hairline.³ Most affected women do not have elevated levels of circulating androgens, and they have normal menses, normal pregnancies, and are not virilized.⁴

Pathophysiology

Androgen processing in hair follicles appears to be different in males and females even though scalp follicles demonstrate similar metabolic pathways.³ Although young females have twice as much 5- α reductase in frontal hair follicles than in occipital hair follicles, levels in the former are still only half those found in young males. Aromatase converts testosterone to estradiol in both males and females, but young females have higher levels of aromatase in scalp hair follicles than their male counterparts. These differences are thought to explain the milder form of androgenetic alopecia and the sparing of the frontal hairline seen in females.⁵

Clinical Evaluation

Hair braiding, hot combing, chronic illness, crash dieting⁶ and nutritional alterations, metabolic and endocrine disorders, stress, environmental changes, surgical procedures, and certain drugs can precipitate or exacerbate alopecia.³ Patients should be asked about their use of exogenous estrogens, progestones, anabolic steroids, and testosterone.

Hyperandrogenism might be suspected if the androgenetic alopecia is of rapid onset (months to one year), there is significant fronto-parietal recession, or there is no

strongly positive family history.⁷ The most common androgen excess syndromes resulting in alopecia are late-onset adrenal hyperplasia, polycystic ovarian disease, and relative estrogen depletion in the perimenopausal female.³

In practice, one only needs to measure testosterone, DHEAS, and prolactin levels if there are menstrual irregularities or infertility, or signs of hirsutism, cystic acne, galactorrhea, or virilization.⁵ If none of these signs are present, no hormonal tests are required but if there is significant hair thinning and other causes need to be eliminated, test TSH.⁵

Treatment

Treatment of female androgenetic alopecia varies from country to country, depending on local preferences and experience, as well as on the availability of some drugs.

• Antiandrogens

Cyproterone acetate (not available in the USA). In Europe, cyproterone is the major drug used for the treatment of androgenetic hair loss in women.⁸ Professor Orfanos' preferred treatment is cyproterone acetate 2 mg (together with ethinylestradiol 50 mcg in Diane[®] or 10-20 mg (Androcur[®]), plus topical application of estrogen containing hair lotions such as Crinohermal[®]. However, the efficacy of estrogen containing hair lotions remains unproven, and they are not approved for use in many countries, including North America. In Canada, 50-100 mg of Androcur[®] are given daily from days 5-14 of the menstrual cycle, while doses of 10-20 mg per day are used for acne but not for alopecia androgenetica in females.⁹

Spiroglactone. In cases where there is androgen excess, spiroglactone (Aldactone[®]) has been effective in doses of 75-200 mg per day.³ Most of the studies have been uncontrolled and conducted in small numbers of patients. Nonetheless, extrapolating data from hirsutism trials, it does appear that a dose of at least 100 mg a day is necessary for efficacy in androgen-mediated hair disorders.

• Minoxidil

Where cyproterone is not approved (as in the USA), minoxidil (Rogaine[®]) may be the treatment of choice. Studies have shown that minoxidil can reduce the extent of hair loss to a cosmetically acceptable degree,¹⁰ and

increase hair weight and number^{11,12} without causing serious or unexpected medical events.¹² In countries where cyproterone is available, minoxidil is less important in treating this condition.

• *5- α Reductase Inhibitors*

Several 5- α reductase inhibitors are in clinical development. *Finasteride* (Propecia[®]) is being studied in male alopecia and in post-menopausal patients with androgenetic alopecia.^{5,9}

• *Hair Transplantation*

In the past, hair transplantation was not widely used because female patients with androgenetic alopecia often have fine, thin hair all over the scalp, and hair loss is not as well demarcated as in men. However, advances in technique have allowed many women, previously thought to be ineligible for surgery, to benefit from this procedure.¹³ The mini- or micrograft technique is useful in women who have very profound thinning in the front of the scalp and have a good density of thick hair in the occiput. Attaining a natural-looking result in female patients is easier because the frontal hairline is usually still present.¹⁴ Expectations must be realistic, and the surgeon must explain carefully what can and cannot be achieved.¹³

Approaches for Patients Unsuitable for Medical or Surgical Treatment

Suggestions kindly provided by Dr. Zoe Draelos, Department of Dermatology, Bowman Gray School of Medicine, Wake Forest University, North Carolina

Scalp Camouflage¹⁵

The contrast between a pale bald scalp and dark hair often accentuates hair loss. The contrast can be minimized by colouring the scalp temporarily with wax crayons or vegetable dyes, or permanently with tattoo pigment.

Cosmetic Hair Techniques¹⁵

Styling should add volume and fullness. Setting tight curls yields more hair fullness; back-combing or teasing can allow the hair to stand away from the scalp creating the illusion of volume. It is important to avoid hair breakage in areas where the hair is already thinned. Styling products such as gels, mousses, and hair sprays also help the hair to stand

away from the scalp but lose their hold each time the hair is wetted or combed and need to be reapplied each time the hair is restyled. Permanent hair waving also increases apparent hair volume; but to minimize damage to the hair shaft, this must be performed with care and with as much time as possible between repeats.¹⁵

Crepe hair can camouflage very small, localized areas of scalp in patients who need an inexpensive, short-term camouflage. Hair pieces can provide extra hair in the frontoparietal region. Hair additions can also be useful to camouflage frontoparietal thinning, but the styling time required can be expensive and the extra weight of the added hair can cause traction alopecia.¹⁵

Permanent dyes can be used to lighten hair colour to blend in better with the pale scalp, but permanent hair dyes are damaging to the hair shaft.¹⁵

Future

Future breakthroughs in the treatment of female androgenetic alopecia may come from application of molecular biology developments to growth factors and to blocking specific receptors with cytokines or antisense oligonucleotides.⁵

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• *Corticosteroids*

Various potent topical formulations (i.e. solutions or creams) of corticosteroids are used to treat scalp psoriasis. Prolonged use can cause the usual, well-recognized problems. Once the patient has improved, treatment should be tapered gradually to reduce the chance of relapse.

Intralesional corticosteroids – Stubborn or persistent or treatment-resistant plaques will usually respond to intralesional corticosteroid injections.^{7,11}
(e.g. 0.1-1 ml of triamcinolone acetonide 2.5-10 mg/ml)

• *Calcipotriol (calcipotriene)*

In a multi-centre, prospective randomized, double-blind, parallel group study in 49 adults, calcipotriol (50 mcg/ml) was well tolerated and significantly superior to its own vehicle used as placebo in reducing redness, thickness, scaliness, and extent of psoriasis.⁶ In another study, betamethasone 17-valerate solution (1 mg/ml) was significantly more effective than calcipotriol (50 mcg/ml) and was associated with statistically significant less local irritation on the scalp and face.¹²

• *Other Treatments*

In severe, recalcitrant scalp psoriasis, it may be necessary to consider systemic therapy with acitretin or methotrexate⁸ combined with topical corticosteroids or vitamin D₃ preparations.⁷ Unfortunately, hair acts as an ultraviolet shield; hence for scalp psoriasis, PUVA therapy is only useful in patients who are significantly bald.⁸ Grenz ray (soft x-rays) therapy has been found to be effective,¹³ but this form of therapy is considered to have unacceptable risks and is no longer used in most countries.

Treatment Regimes

When scaling is thick and adherent, it must be removed by overnight application of a keratolytic. Dr. Kenneth Arndt uses a phenol/saline lotion (P & S liquid).¹¹ Professor Gollnick uses salicylic acid (up to 15%) oil formulations, applied for 12-24 hours under occlusion.⁷ Professor Kragballe prescribes a daily application of 5% tar and 5% salicylic acid in petrolatum.¹⁴ The scalp should be shampooed daily. Once the crust/scale is removed, the keratolytic can be used as necessary to keep the scalp reasonably free from scaling. After shampooing, an

appropriate potent corticosteroid formulation should be massaged into the scalp. Dr. Arndt uses clobetasol scalp solution or cream. In order to achieve and maintain a good response, he often finds it necessary to use combination therapy and to substitute topical anthralin or calcipotriene for the corticosteroid.¹¹ If appropriate, other options such as tar preparations or the milder topical corticosteroids can be substituted.⁷

Practice Tips for Treating Scalp Psoriasis

1. Keep the hair cut short⁵ when appropriate.
2. Thick and adherent scaling must be removed by a keratolytic.
3. Tar or anthralin preparations are unsuitable for patients with white or grey hair.
4. Shampoo daily.
5. Highly potent corticosteroids are often required in the early stages of treatment.
6. Stubborn or treatment resistant plaques will usually respond to intralesional corticosteroids.^{7,11}
7. It is often necessary to rotate various treatments.¹¹
8. Carefully instruct the patient.¹⁴ Positive reinforcement is also very important – patients must believe that they can be helped.

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
<i>Antifungal</i>	Amphotericin B Lipid Complex Injection Abelcet® <i>Liposomes</i>	Approved by the FDA for the treatment of any progressive form of fungal infection that fails to respond to conventional treatment. This is in addition to its indication for aspergillosis.
	Butenafine HCl Cream 1% Mentax® <i>Schering/Penederm</i>	Approved by the FDA on October 18, 1996 for the topical treatment of interdigital tinea pedis (athlete's foot).
	Itraconazole Sporanox® <i>Janssen (Johnson & Johnson)</i>	Approved by the FDA on December 6, 1996 for the "pulse treatment" of onychomycosis of the fingernails. Available in 100 mg capsules. The dose is 200 mg twice daily for the first week of each month for two months. (The dose of 200 mg daily given for 12 weeks for onychomycosis of the toenails is already established.)
<i>Antipsoriatic</i>	Acitretin Soriatane® <i>Roche</i>	Approved by the FDA on October 28, 1996 for the treatment of severe recalcitrant psoriasis. Soriatane® will be available in 10 and 25 mg tablets.
<i>Antiviral</i>	Penciclovir cream 1% Denavir® <i>SmithKline Beecham</i>	Approved by the FDA for the treatment of recurrent herpes labialis. This is the first topical antiviral cleared for this indication in the USA.
	Valacyclovir Valtrex® <i>Glaxo-Wellcome</i>	The FDA has approved valacyclovir for the new indication of treating first episode genital herpes. This indication is also approved by the Canadian HPB.
<i>Hair transplantation</i>	Laser device Sharplan Silktouch laser® <i>Laser Industries</i>	Received marketing approval from the FDA early this month. It is claimed to be the first such technology to be approved by the FDA for use in installing hair plugs.
<i>Head lice prophylaxis</i>	Permethrin lotion Nix® <i>Warner-Lambert</i>	Permethrin was recently approved by the FDA for prophylactic use during head lice epidemics. OTC.
<i>Parasitic infections</i>	Ivermectin Mectizan® (6 mg tablet) <i>Merck</i>	Approved by the FDA on November 22, 1996 for the treatment of strongyloidiasis and onchocerciasis. *Undergoing clinical trial for human scabies.

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