Liposome encapsulation improves efficacy of betamethasone dipropionate in atopic eczema but not in psoriasis vulgaris

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Summary. The effect of a liposomal preparation of betamethasone dipropionate (0.039%, BDP) has been compared to that of a commercial propylene glycol-gel containing 0.064% BDP in a double-blind, randomized, paired trial lasting 14 d in 10 patients with atopic eczema and 10 patients with psoriasis vulgaris.

In eczema, the liposome preparation tended to reduce erythema and scaling more than the conventional gel, the difference in the latter parameter being significant on Day 7. There was greater improvement of psoriasis on the side treated with the reference gel.

Hence, liposome encapsulation of BDP may increase the antiinflammatory action but not the antiproliferative effect. Since inhibition of mitotic activity is linked to the atrophogenicity of topical corticosteroids, the results suggest that liposome encapsulation may improve the benefit-risk ratio in eczema.

Key words: betamethasone dipropionate, eczema; atopic eczema, psoriasis vulgaris, liposomes, gel, therapeutic efficacy

Liposomes are frequently considered as drug delivery systems for systemically applied chemotherapeutic agents and anticancer drugs (reviewed in 1, 2). Topical administration of liposome preparations to the skin has recently received attention, and studies have been performed with topical glucocorticoids [3–8], tetracaine [9] and econazole [10]. In 1988, the latter product has been registered in Switzerland (Pevaryl®-Lipogel, Cilag Corp.).

Pharmacokinetic evaluation of triamcinolone acetonide [3, 4] and hydrocortisone [6–8] showed higher drug levels in the skin and lower systemic availability following application of liposomal corticosteroids as compared to conventional preparations. However, this did not appear to be any data on the influence of liposomal encapsulation on corticosteroid activity. The present study was a comparison of the effects of a gel and a liposome preparation of betamethasone dipropionate (BDP).

Materials and methods

The controlled double-blind studies were approved by the local Ethical Committee. Twelve out-patients with atopic eczema and 11 with psoriasis vulgaris took part in the study after giving voluntary written informed consent to it. Ten patients in each group finished the study; atopic eczema 10 females aged 33 (13) y, psoriasis vulgaris 8 f and 2 m aged 36 (16) y. Exclusion criteria were > 40% body surface area affected, pre-treatment with glucocorticoids within the last 5 days, pregnancy and lactation. Facial lesions were not treated with the study medication.

The patients were randomized to receive the liposome preparation on one side of the body and the reference gel on the other. Medication was applied to the affected areas without occlusion once daily for 14 days. In addition to the study medication the patients were allowed to use a non-medicated preparation at an interval of 12 h. In eczema a cream (Vobaderm® Basiscreme, Hermal, Reinbek, F.R.G.) and in psoriasis an ointment were offered (Psoralon® Fettcreme, Hermal).

Following the initial evaluation, patients returned for follow-up at 4, 7 and 14 days. At every visit the investigator clinically rates symptoms and signs: eczema-itching, erythema, oedema, vesicles, papules/nodules, exudation, scaling, lichenification, excoriation, and fissures; psoriasis-erythema, large and small infiltrates, scaling; scored as 0 (none), 1 (mild), 2 (moderate), 3 (severe), or 4 (very severe). In addition, the global effect was rated 0 (healed), 1 (major improvement), 2 (moderate improvement), 3 (minor improvement), 4 (no change), 5 (worse). At the follow-up visits the patients were also asked about side-effects.

The liposome preparation was a polyacrylate gel containing 0.039% betamethasone dipropionate (BDP) encapsulated in unilamellar liposomes with a mean diameter of 30 nm. Liposomes were produced from egg lecithin by detergent dialysis [11]. A conventional 0.064% betamethasone dipropionate gel containing propylene glycol (Diprosis® Gel, Essex Pharma, Munich, F.R.G.) was used as the control.

Data are expressed as arithmetic mean (SEM). Differences in treatment results were evaluated for significance using the Wilcoxon rank sum test for matched pairs. P ≤ 0.05 was considered statistically significant.
Results

Liposome-encapsulated BDP 0.039% was at least equipotent to the 0.064% commercial gel in the treatment of atopic eczema (Fig. 1). Erythema, scaling and itching presented by all patients improved by 77, 74 and 85% following the liposome BDP, and by 62, 50 and 84% with the reference preparation. The liposome product tended to clear erythema and scaling more rapidly. The difference reached significance on Day 7 for the latter parameter. Excoriation, also found in all subjects, improved by 83% (liposome BDP) and 92% (P > 0.05).

Papules/nodules (9 subjects), lichenification (n = 6) or fissures (n = 4) presented by the subjects responded by 67 to 83% on the sides treated with the liposome preparation, and by 77 to 83% on the other side. Oedema (one patient) and exudation (n = 2) were cured within 4 days following either treatment. With either preparation two patients were cured and in the others major or moderate improvement was seen within 14 days (Fig. 1).

In contrast, the commercial BDP formulation was superior in the treatment of psoriasis (Fig. 2). It cured one patient, major improvement was obtained in three and a minor to moderate one in six. Liposomal BDP induced minor (6 subjects) to moderate (4 patients) improvement of psoriasis. The reference gel was superior in six patients and the liposome preparation in one. Differences were observed in the signs of the disease. Erythema, large and small infiltrates and scaling improved by 9 to 33% following the liposome product and by 31 to 47% following the gel. A significant difference was seen in erythema and large infiltrates (Fig. 2).

One patient with psoriasis was excluded from the study on Day 7 due to major pruritus on the side treated with the liposome product. Dryness of the skin was claimed by one subject on the side receiving the gel, and another showed folliculitis on both sides.

Side-effects were reported by five patients with eczema. Three presented papules and/or postules on both sides. Major dryness of the skin was reported by one patient following liposomal BDP and by two following the gel.

One patient with atopic eczema was removed from the study due to a common cold, and another did not report to the hospital for the follow-up visits.

Discussion

Liposomes have many potentially useful properties as drug delivery systems. Liposomes can adsorb to almost any cell type and once adsorbed they can be endocytosed, after which the drug is released into the cell. Fusion of adsorbed liposomes with cells, too, may lead to a high intracellular drug level. In addition, liposomes can release incorporated drugs close to the adsorbing cell [12].

The use of liposomes in dermatology has recently been reviewed [12]. Liposomes may serve to improve topical therapy of skin disease. Due to the barrier function of the horny layer, current vehicles are only marginally effective in delivering active ingredients to the site of disease [13], and absorption rates amount only to a few percent [14].

In the case of topical glucocorticoids, systemic side-effects may be reduced by slow drug release, which might result in improved biotransformation to inactive metabolites. As the value of super-potent glucocorticosteroids