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Topical 15% Undecylenic Acid (UDA) Cream vs Placebo (PLB): A Canadian, Randomized, Multicenter, Patient-Initiated (PI) Trial in Patients with Recurrent Oral-labial (OL) Herpes Simplex Virus (HSV) Infections. SL Sacks, S Shafran, FY Aoki, DLJ Tyrrell, W Schlech, J Mendelson, D Rosenthal, MJ Gill, I Chang, R Bader. U British Columbia, Vancouver, BC, Canada, Canadian Cooperative Study Group, Fisons Pharmaceuticals, Rochester, NY, USA.

Effective therapy for OL HSV is not available. Because UDA has improved the clinical course of HSV-1 infections in animals, we conducted a PI trial of 15% UDA cream in the early, prodromal therapy of OL HSV. Following double-blinded randomization, volunteers with prodromal symptoms in ≥75% of episodes were instructed to apply the study material 5 or 6 times daily and to report for exam/culture within 30h of first treatment. Daily investigator assessments were conducted, thereafter, until lesions were fully crusted. Treatment applications were reduced to thrice daily and assessment to alternate days after crusting. A total of 573 patients applied the study material to an active episode in 8 study centers. Of these, 560 were efficacy-evaluable, of whom 293 received UDA and 267 PLB. PLB recipients who were culture positive during the study episode experienced substantially longer times to healing [7.8 vs 3.3 days; $P<0.001$], crusting [2.0 vs 1.4 days; $P=0.006$] and loss of symptoms [5.1 vs 3.0 days; $P<0.001$] compared with their culture-negative counterparts. Starting point identity was achieved between treatment groups with regard to age, gender, HSV frequency, usual lesion severity, actual entry lesion and rate of nonlesional prodromes. Mean times to healing were 7.0 days for UDA recipients vs 6.6 days for PLB recipients [$P=0.14$]. Mean times to crusting were 1.8 days for UDA recipients compared with 1.9 days for PLB recipients [$P=0.21$]. Mean maximum lesion sizes were 34.4 mm^2 and 34.2 mm^2 for UDA and PLB, while mean times to loss of pain and tenderness were 4.7 and 4.5 days, respectively. Mean durations of viral shedding, however, were 1.2 days in UDA recipients vs 1.8 days in PLB recipients ($P<0.001$). Minor adverse reactions were observed frequently in UDA recipients, where 72% complained of burning on drug application compared with 13% for PLB recipients. In this, the largest trial of OL HSV infection reported to date, culture-confirmed OL HSV was longer and more severe than culture-negative. Despite significant antiviral effects of topical PI 15% UDA cream, significant clinical benefits were not observed for patients with OL HSV and minor burning was a frequent adverse effect.

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Cutaneous Reactions to Combination Zidovudine-Probenecid Treatment

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Eight male patients with human immunodeficiency virus (HIV) infection being treated with zidovudine were entered into a four-week study to determine if the established beneficial effect of probenecid on zidovudine pharmacokinetics would continue beyond the six-day period previously studied, and whether the combination would be safe and well tolerated over four weeks. The subjects had no serious hepatic or renal dysfunction, received no other drug known to affect the metabolism or excretion of zidovudine, and gave written informed consent. When probenecid treatment was initiated at 500 mg every 8 hours, the zidovudine dosing interval was extended from four to eight hours at the same individual dosing, thereby reducing the total daily zidovudine dose by one-half. The probenecid and zidovudine were taken on the same eight-hourly schedule (8 a.m., 4 p.m., 12 midnight). Over the course of treatment with the combination, six of the eight subjects developed a cutaneous rash of some degree. Two subjects developed minimal rashes during the first week which were localized to the trunk and resolved despite continued treatment. Three of the subjects had a generalized maculopapular erythematous eruption with myalgias, malaise and/or fever. One other subject had an extensive rash without symptoms, and these four subjects with extensive eruptions had their treatment discontinued during the second week. Skin biopsy of two subjects showed intradermal perivascular mononuclear infiltration compatible with a drug eruption. The rashes all resolved with discontinuation of probenecid and resumption of the previous four-hourly dosing of zidovudine. We believe that the unexpectedly high incidence of skin rash and associated symptoms in our patients represents an adverse drug reaction to probenecid, not a chance event, and may be similar in mechansim to the cutaneous eruptions seen in HIV-infected patients treated with co-trimoxazole.