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Research Article

Pilot Study to Evaluate the Safety and Therapeutic Efficacy of Topical Oxifulvic Acid in Atopic Volunteers

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Strategy, Management and Health Policy				
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ABSTRACT The study objectives were to establish first the safety and second the therapeutic efficacy of topically applied oxifulvic acid compared to 1% hydrocortisone and placebo creams. Oxifulvic acid has established antiinflammatory properties in vitro. It also inhibits elicited ear inflammation in mice at concentrations of 4.5 and 9%. In this double-blind cross-over study, 23 healthy volunteers allergic to grass or house dust mite allergen were recruited and included after signing informed consent. During the initial run-in period all volunteers were randomized to apply either 4.5 or 9% oxifulvic acid for 2 weeks on the volare aspect of one forearm (100 mm diameter) and rechallenged 21 days later to establish sensitization. Thereafter, volunteers were randomized to either placebo. 1% hydrocortisone, 4.5 or 9% oxifulvic acid creams. Creams were applied under occlusions 1 h prior to intradermal allergen challenge and every 8 h thereafter for 3 days (21-day intervals). The surface areas of the immediate and late phase skin reactions were calculated. Liver and kidney function tests as well as full blood counts were done at screening and thereafter weekly for the first 2 weeks and then at each follow-up visit. Topically applied oxifulvic acid had no significant effect on any of the safety parameters and also did not induce sensitization when applied on the skin. Oxifulvic acid (4.5%) caused inhibition of the elicited inflammatory reaction at 15 min and differed significantly from the 9% cream at 24 h. These changes were similar to that caused by hydrocortisone. No other significant changes were detected. Drug Dev. Res. 57:40–43, 2002.

Key words: oxifulvic acid; atopy; safety

INTRODUCTION

Fulvic acid is one of the components of the so-called humic substances which are naturally formed during thc decay of plant and animal residues [MaCarthe et al., 1985]. Humic substances can be divided into humic acid, fulvic acid, and humin, based on their solubility in water. Humic acids are known to have some therapeutic benefit and have been used for the treatment of various diseases such as inflammation, hypercholesterolemia, and Von Willebrand's disease [Salz, 1974; Solovyeva and Lotosh, 1984; Lopez-Fernandez et al., 1992]. The evidence for therapeutic use of fulvic acids is, however, sparse. In vitro experiments [Wang et al., 1996] found that fulvic acid from peat possesses free radical scavenging properties.

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A unique process was created to convert bituminous coal by controlled wet oxidation in high yield to high-quality humic and fulvic acids. To distinguish these synthesized products from the naturally occurring substances they are called oxihumic and oxifulvic acid [Berg et al., 1997].

Oxifulvic acid has been shown in vitro to have antimicrobial activity [Van Rensburg et al., 2000] and to suppress superoxide production by neutrophils. Topical application of oxifulvic acid to laboratory mice demonstrated clear antiinflammatory properties [Van Rensburg et al., 2001]. Extended safety and toxicity testing on experimental animals have also shown no acute or chronic toxic reactions (J.R. Snyman, unpubl.).

The aim of the present study was to investigate the safety and tolerability of topically applied oxifulvic acid (4.5% and 9%) in healthy human volunteers (history of allergy to grass pollens and or house dust mite but otherwise healthy) with efficacy as a secondary outcome, i.e., inhibition of the cutaneous hypersensitivity reaction after intradermal antigen administration.

MATERIALS AND METHODS

In a double-blind cross-over study, 23 atopic volunteers allergic to grass pollen were randomized to receive placebo UEA cream or 1% hydrocortisone, or 4.5% oxifulvic acid or 9% oxifulvic acid cream on alternating forearms in each application, applied over an elicited cutaneous hypersensitivity reaction. The volunteers were all otherwise healthy with no prior history of drug allergy and were enrolled after signing informed consent. The study protocol was approved by the University of Pretoria Faculty of Health Sciences Research Ethics Committee.

In order to investigate the possible development of sensitization to oxifulvic acid, volunteers received either 4.5% or 9% oxifulvic acid on intact, non-inflammed forearm skin over a 14-day period (i.e., three applications of 100 cm^2/day). Rechallenge 21 days later was done with 9% oxifulvic acid cream on the same skin area to test for sensitization. During this period kidney and liver functions were evaluated at baseline and thereafter weekly for the first 2 weeks and then again at the next rechallenge. The same safety bloods were again collected on each of the following four tests sessions.

After the initial sensitization testing, the volunteers received an intradermal administration of antigen (i.e., 0.05 ml Southern Grass Mix® or house dust mite antigen; Bayer DHS division, Bayer (Pty), Isando, South Africa; equal to 10 PNU) on alternate forearms at 21-day intervals for a total of four episodes, corresponding with the four different study cream applications. Study creams were applied under occlusion for 1 h prior to antigen administration and thereafter every 8 h for 48 h.

The surface areas of the immediate wheal and flare and late phase skin reactions were calculated by marking the perimeters of these reactions on transparent plastic film at 0.25, 1, 6, and 24 h after intradermal antigen administration. This is an established method for evaluating the immediate cutaneous hypersensitivity reaction [Snyman et al., 1995].

Statistical Analysis

An ANOVA technique was used to detect differences within groups over time as well as to test for significant changes between groups on the various treatment regimens. Significance was established at the 5% level throughout the study.

RESULTS

There were no clinically significant changes in any of the safety parameters evaluated over the entire study period. Two volunteers withdrew from the study due to systemic reactions following the first intradermal antigen challenge and a further two stopped participation due to a lack of compliance with the study medication.

None of the volunteers developed sensitization to the oxifulvic acid and tolerated the cream well. There was no difference in side effects reported from placebo and no side effects due to cream application were reported in any of the study arms. See Figs. 1 and 2 for a summary of data on kidney and liver functions and full blood counts.

Oxifulvic acid resulted in slight inhibition of the elicited inflammatory reaction at 15 min and differed significantly from the 9% cream at 24 h. These changes were similar to that caused by hydrocortisone cream. No other significant changes were detected (see Fig. 3 for details).

DISCUSSION

In this study topically applied 4.5% and 9% oxifulvic acid did not differ from placebo (UEA) cream with regard to their side-effect profile. The test creams were also shown to be well tolerated and nonirritating and nonallergenic, confirming in vivo animal data [Van Rensburg et al., 2001].

The 4.5% oxifulvic acid cream also demonstrated some antiinflammatory properties similar to that demonstrated by 1% hydrocortisone cream. The fact that it was not possible to show the same results with the 9% cream possibly is reflective of its physicochemical properties, i.e., being more acidic in the cream. This low pH may explain poor skin penetration and therefore poor efficacy. The mechanism for oxifulvix acids in vivo activity was not investigated in this study

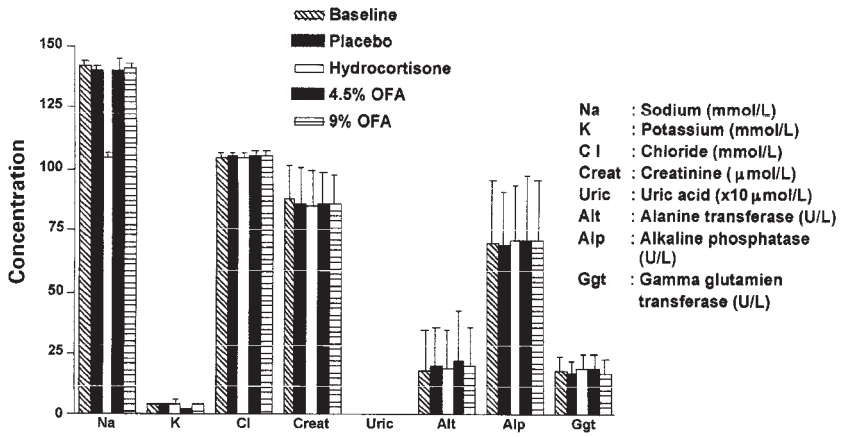

Fig. 1. Kidney and liver functions of volunteers during the trial.

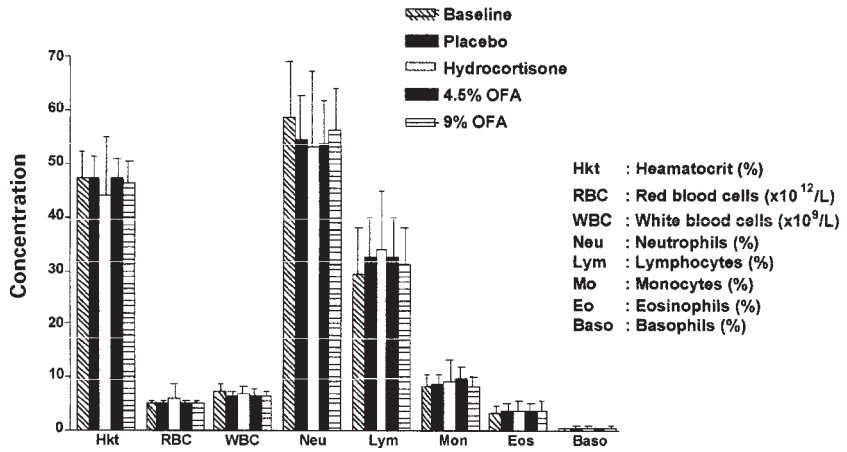

Fig. 2. Full blood counts of volunteers during the trial.

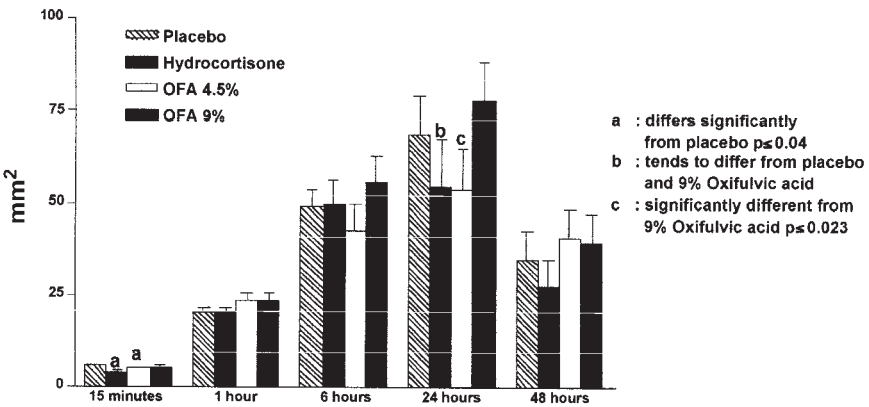

Fig. 3. Effects of a 24-h treatment of oxifulvic acid on elicited inflammatory reaction.

but in vitro studies have documented free radical scavenging properties [Wang et al., 1996] as well as inhibition of interleukin 2 production (J.R. Snyman, unpubl.). The contributions of these properties to oxifulvic acid's antiinflammatory effects need to be further explored before speculation on its pharmacodynamics is possible. The fact that oxifulvic acid cream in an animal model had similar antiinflammatory

properties as betamethasone (0.1%) and diclophenac (1%) creams [Van Rensburg et al., 2001] are perhaps indicative of it inhibiting specific immune modulators rather than only a nonspecific scavenging of free radicals.

In conclusion, oxifulvic acid is safe and well tolerated when applied topically on uninflammed and inflamed skin. This study also confirmed its antiinflammatory properties seen in animal studies [Van Rensburg et al., 2001]. The latter finding needs to be further explored utilizing different vehicles for active substance delivery to the skin and in various other models of inflammation in larger studies to reconfirm the above findings in humans.

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