Pharmacologic and Clinical Effects of Lonapalene (RS 43179), a 5-Lipoxygenase Inhibitor, in Psoriasis

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The pharmacologic and clinical effects of the 5-lipoxygenase inhibitor, lonapalene, have been determined in a double-blind, placebo-controlled, topical study in ten volunteers with psoriasis. A statistically significant clinical improvement was seen in lesions treated with 2% lonapalene ointment as compared with vehicle-treated sites. Although there was a statistically significant reduction in the levels of material similar or identical to the chemoattractant arachidonate 5-lipoxygenase product, leukotriene B_4, in skin chamber fluid samples from lonapalene versus vehicle treated lesions, no significant reduction in arachidonic acid or 12-hydroxy-5,8,10,14-eicosatetraenoic acid was seen. The reduction in leukotriene B_4 equivalents occurred before significant clinical improvement in lesions was seen. This and the selectivity of the pharmacologic response suggest that the therapeutic effect of topical lonapalene in psoriasis might be related to inhibition of leukotriene B_4 synthesis. These results support the view that 5-lipoxygenase inhibitors may be useful in the treatment of psoriasis, and that leukotriene B_4 is a relevant mediator of the pathology of this disease. *J Invest Dermatol 95:50–54, 1990*

Determination of the relevance of a locally produced biologically active substance in the pathogenesis of a disease process requires the satisfaction of certain criteria, most of which demand in vivo experimentation. As previously reviewed [1], these criteria include 1) demonstration of the release of the substance in vivo by analysis of samples from the disease process; 2) demonstration that the substance is able to reproduce in vivo, in appropriate doses, that aspect of the disease process for which it is thought to be responsible; 3) demonstration of mechanisms for the local production of the substance; and 4) demonstration that specific inhibitors of the formation or effects of the substance, administered in vivo, elicit appropriate therapeutic responses. Further useful information concerning the pathogenic importance of a substance in a particular disease may be obtained by determining the specificity of production of the substance to the disease, and by determining the relative amounts of other compounds with similar biologic properties in samples from the disease process.

The arachidonic acid (AA) 5-lipoxygenase metabolite, leukotriene B_4 (LTB_4) has been implicated in the pathogenesis of psoriasis for several reasons. It possesses potent neutrophil chemoattractant properties in vitro [2,3] and has been identified in samples from psoriatic lesions in concentrations significantly higher than in those from clinically normal skin [4–7]. Furthermore, topical application of LTB_4 to the skin of normal volunteers induces the formation of intraepidermal neutrophil microabscesses, mimicking to some extent the inflammatory infiltrate in psoriatic lesions [8]. While this evidence supports a role for LTB_4 in psoriasis, other findings suggest that its local production is unlikely to be a primary pathogenic phenomenon. These include the fact that its formation is not specific to psoriatic lesions, LTB_4-like material having been recovered from atopic dermatitis [7] and allergic contact dermatitis [9]. Furthermore, single and multiple applications of LTB_4 to the skin of normal volunteers and to the clinically uninvolved skin of patients with psoriasis failed to elicit psoriatic lesions, multiple applications being associated with a localized state of decreased responsiveness [10]. Finally, LTB_4 is not the only neutrophil chemoattractant isolated from psoriatic lesions. Also recovered were biologically active amounts of 12-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE) [11,12], especially the 12(R)-isomer [13]; platelet activating factor [14,15]; C5a des arg-like material [16,17,18]; an unidentified monohydroxy fatty acid-like chemokinetic lipid [19]; and a group of novel chemoattractant cytokines [17,18,20] which appear to be related to interleukin 8 [21]. While these findings suggest that local release of LTB_4 is not a primary pathogenic phenomenon in psoriasis, they do not exclude the possibility that LTB_4 may play an important role, together with other phenomena, in a combination of events that culminate in a psoriatic lesion. The importance of 5-lipoxygenase in psoriasis is also enhanced by the finding of increased levels of the vasoactive sulphidopeptide 5-lipoxygenase products, LTC_4 and D_4, in samples from psoriatic lesions [22].

Of the various criteria described above, one of the most difficult to satisfy is that requiring demonstration of an appropriate therapeutic response following in vivo administration of mediator specific synthetase inhibitors or receptor antagonists. Difficulties arise because of the lack of pharmacologically specific agents of sufficient proven safety for clinical use. Furthermore, compounds which exhibit appropriate pharmacologic effects in the laboratory may lack these effects when administered to humans. For example, L652,343, an active 5-lipoxygenase inhibitor in vitro, failed to reduce LTB_4 levels in samples from lesions when administered orally to volunteers with psoriasis [23]. Therefore, it becomes important to determine whether the administration of a specific synthetase inhibitor not only causes reduction in the lesional levels of the appropriate mediator, but also whether any reduction occurs prior to the onset of a significant therapeutic response, such that the therapeutic

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response may possibly be attributed to inhibition of synthesis of the mediator.

Lonapalene (6-chloro-2, 3-dimethoxynapthalene-1,4-dio-diacetate, RS 43179) inhibits the production of 5-lipoxygenase metabolites by ionophore-stimulated human polymorphonuclear leukocytes and by high-speed supernatants from rat basophilic leukemia cells with IC_{50} values of approximately 20 and 0.5 μM, respectively [24]. Topically applied lonapalene also caused dose-dependent inhibition of AA-induced mouse ear oedema [25]. In contrast, concentrations up to 200 μM were inactive or slightly stimulatory towards human platelet, sheep vesicular gland, and mouse epidermal cyclooxygenase, platelet and mouse epidermal 12-lipoxygenase, and soya bean 15-lipoxygenase [24]. Topical application of lonapalene in a Scholtz-Dumas bioassay [26] in volunteers with psoriasis demonstrated antipsoriatic activity [25]. This effect was confirmed in double-blind therapeutic trials, in which lonapalene appeared to be as efficacious as a potent steroid [27,28].

We now report the results of a double-blind, placebo-controlled, integrated pharmacologic and clinical study, in which the levels of LTB_4, 12-HETE, and their precursor, AA, have been measured in samples from psoriatic lesions during treatment with topically applied lonapalene. To our knowledge, this is the first reported study of its kind, with a 5-lipoxygenase inhibitor, either in disease of the skin or any other human organ.

MATERIALS AND METHODS

Patients Nine male patients and one female patient, aged 21–57 years (mean, 44.4 years), participated in the study. All had had psoriasis for at least one year, and the lesions involved 10%–40% of the body surface. The patients had not received systemic treatment for their psoriasis at any time, and had not applied any active topical therapy for 2 weeks prior to the study, using only emulsifying ointment BP as an emollient and soap substitute. No systemic medication of any kind was taken during the trial. Ethical committee approval was granted and informed consent obtained from each volunteer before the study.

Treatment Lonapalene ointment (2% w/w) and its placebo vehicle containing propylene glycol, propylene carbonate, glyceryl monostearate, white wax, and petrolatum were used. Symmetrical areas of at least 100 cm^2 on the limbs were designated for paired comparison. Patients were supplied with color-coded tubes, and active drug and placebo were applied in a randomized, double-blind manner to the designated symmetrical lesions. Paired applications were made by the patients twice daily without occlusion for 28 d, and the patients were asked to wash their hands after each application. An untreated lesion sited at least 10 cm away from the test areas was also observed in each case. The designated areas were not exposed to sunlight during the study, and bland emollient was applied to other areas only if necessary.

Double-Blind Clinical Assessment Before treatment, and on days 4, 14, and 28 after starting treatment, each designated area was evaluated visually for erythema, induration, and scaling by the same investigator throughout the study. Each sign was arbitrarily scored on a scale from 0–3 (0 = no abnormality, 1 = mild, 2 = moderate, and 3 = severe changes), allowing a combined maximal score of 9 per designated site. Each patient also underwent routine haematologic and biochemical testing and urinalysis immediately before and after the trial.

Lesion Sampling On days 4 and 14 after starting treatment, designated lesions were sampled by using a skin chamber method, as previously described [5]. Briefly, lesions were gently abraded with a scalpel blade to yield a 2-cm diameter glistening area with minimal punctuate bleeding. An acrylic cylindrical chamber (19 mm internal diameter) was fixed to each abrasion with cyanoacrylate adhesive and 1 ml sterile phosphate-buffered saline (PBS) added. This was discarded after 5 min and replaced with a further 1 ml PBS for 30 min. Two chamber fluid samples were obtained from each designated area at each time point, pooled, and immediately centrifuged to remove blood cells. Supernatant was divided into two 0.9 ml samples (A and B), one of which (A) was mixed with deuterated internal standards (100 ng [5,6,8,9,11,12,14,15-^{2}H] AA and 2 ng [5,6,8,9,11,12,14,15-^{2}H] 12-HETE dissolved in 20 μl methanol). Both samples were then snap frozen in liquid N_2 and stored at −20°C.

Sample Purification and Assay Each sample containing deuterated internal standards (A) was thawed, acidified with 25 μl glacial acetic acid, and partitioned three times with 0.8 ml ethyl acetate. The organic phases were separated by centrifugation, pooled in silanized glassware, and evaporated under a stream of N_2. Following vacuum desiccation for 30 min, the residue was redissolved in 1 ml methanol and partitioned twice with 1.3 ml n-heptane to remove non-polar material. The upper hexane phases were discarded and the methanolic layer evaporated under a stream of N_2. The residue was purified by reversed-phase high-performance liquid chromatography (HPLC) on a 25 cm × 4.9 mm Nucleosil 5 C18 column (Hichrom, Reading, UK) eluted with methanol/water/acetic acid (93:7:0.01, by vol) at 1 ml min^{-1}. A 1-min fraction (elution time approximately 4.5 – 5.5 min) coeluting with standard 12-HETE and a 1.6-min fraction (elution time approximately 8.4 – 10 min) coeluting with standard AA were collected. The 12-HETE fraction was evaporated and repurified by straight phase HPLC on a 25 cm × 4.9 mm Nucleosil 50 – 5 μm column (Hichrom, Reading, UK) eluted with hexane/propan-2-ol/methanol/acetic acid (95:3:2:0.1 by vol) at 1 ml/min^{-1}. A 1-min fraction (elution time approximately 5 – 6 min) coeluting with standard 12-HETE was collected. Fractions containing the purified AA and 12-HETE were evaporated and reacted with ethereal methanolic diazomethane followed, in the case of 12-HETE samples by *bis*-trimethylsilyltrifluoroacetamide (BSTFA), to yield arachidonic acid methyl ester and 12-HETE methyl ester trimethylsilyl ether (MeTMS) derivatives. The endogenous AA and 12-HETE in these samples was quantified by stable isotope dilution selected ion monitoring gas chromatography–mass spectrometry (GCMS). GC was carried out on a 25 m × 0.32 mm Hewlett Packard non-polar phase (SE30 equivalent) silica column interfaced with a VG 305 mass spectrometer. Data were recorded under electron impact conditions at 45 eV. The ions monitored were m/z 295 and 301 for the MeTMS derivatives of 12-HETE and its deuterated internal standard and m/z 361 and 369 for the methyl ester of AA and its deuterated internal standard, respectively. The absolute amounts of endogenous AA and 12-HETE in each sample were determined by reference to standard calibration curves.

The second chamber fluid sample (B) from each site was acidified, extracted with ethyl acetate, and partitioned between n-heptane and methanol as described above. The methanolic residue was purified by reversed phase HPLC on the above column eluted with methanol/water/acetic acid (85:15:0.01, by volume) at 0.8 ml/min^{-1}. A 1.5-min fraction co-eluting with standard LTB_4 (approximately 5.8 – 7.3 min) as well as a 1.5-min blank fraction eluting immediately after this were collected. Because ng amounts of standard LTB_4 were injected during column calibration, but pg amounts of endogenous LTB_4 activity recovered from chamber fluid samples, care was exercised to avoid contamination of HPLC injection apparatus with standard LTB_4. Following evaporation and vacuum desiccation, fraction residues were redissolved in 0.3 ml minimal essential medium (MEM) buffered with 30 mM HEPES and 0.1 ml aliquots assayed in duplicate without further dilution and after fivefold dilution in an agarose microdroplet neutrophil chemokinesis assay [12,29]. The LTB_4 equivalents in each sample were determined by reference to standard LTB_4 dose response curves (3 – 100 pg LTB_4 per assay), the value obtained for the blank fraction being subtracted from that obtained for the fraction coeluting with standard LTB_4. All samples from the same volunteer were quantified in the same microdroplet assay.

As no internal standard was used in the LTB_4 assay, correction for losses during extraction and purification could not be made. Experiments to determine the recovery of standard LTB_4 and the interas-

say co-efficient of variation were therefore carried out. Standard LTB_4 (100 pg) was added to 1 ml PBS, which was acidified, extracted into ethyl acetate, partitioned between n-heptane and methanol, and purified by reversed phase HPLC as described above for the LTB_4 analysis. Blank fractions and fractions coeluting with standard LTB_4 (1.5 ml each) were collected and LTB_4 equivalents quantified as described.

Reversed phase HPLC of lonapalene itself showed that it eluted at approximately 6.8 min in the HPLC system used for purification of LTB_4 and would therefore contaminate the fractions (approximately 5.8 – 7.3 min) collected for LTB_4 analysis. It was therefore necessary to determine whether lonapalene affected the responses to LTB_4 in the agarose microdroplet assay. Saturated solutions of lonapalene were prepared by sonicating an excess of crystalline lonapalene in HEPES-buffered MEM for 15 min. Following centrifugation, supernatant was used as medium in the microdroplet assay after 2- to 16-fold dilution, and responses to 100 pg LTB_4 were compared with those seen in the absence of lonapalene. In further experiments, four normal male volunteers (aged 25 – 44 years) each applied 2% lonapalene ointment twice daily to a fixed area of the anterior thigh, for 5 d. After this time a chamber fluid sample (1 ml) was obtained from the lonapalene treated area, acidified, extracted, and purified by reversed phase HPLC as described for the LTB_4 analysis above. Following evaporation and vacuum desiccation of the 1.5 min HPLC fraction, which coeluted with standard LTB_4, 180 pg standard LTB_4 was added to each residue that was redissolved in 0.3 ml HEPES-buffered MEM. Aliquots (0.1 ml, each containing 60 pg LTB_4) were assayed in duplicate in the agarose microdroplet assay and the responses compared with those seen in a standard LTB_4 dose-response curve. These experiments were designed with the knowledge that chamber fluid samples from normal skin contain either no measurable LTB_4 or only trace amounts [5].

Statistical Analysis The significance of the difference between clinical scores for erythema, induration, and scaling was determined by Wilcoxon's Signed Rank Test for non-parametric paired data. Paired t tests were used to compare the levels of AA, 12-HETE,and LTB_4.

Materials LTB_4 was a gift of Dr. J. Rokach (Merck Frosst, Pointe Claire-Dorval, Canada). Racemic 12-HETE, racemic [5,6,8,9,11,12,14,15-^{2}H] 12-HETE and [5,6,8,9,11,12,14,15-^{2}H]AA were prepared by Dr. P. M. Woollard, as previously described [29,30]. 2% Lonapalene ointment, ointment base, and crystalline lonapalene were supplied by Syntex Research (Maidenhead, UK). AA (99% purity), BSTFA, MEM, and HEPES were purchased from Sigma (Poole, UK). Diazald for diazomethane generation and n-heptane were obtained from Aldrich (Gillingham, UK), and all other solvents (HPLC grade) from Fison's (Loughborough, UK).

RESULTS

One patient was removed from the study on day 4 because of the onset of burning, tenderness, swelling, lesional erosion, and perilesional erythema with follicular accentuation in one site, subsequently shown to be the lonapalene-treated area. One other patient developed erythema and pruritus in the lonopalene-treated site between days 24 and 28 of the study, but this was not sufficiently severe to necessitate withdrawal. In the nine patients completing the study, clinical grading showed that the summed scores for erythema, induration, and scaling decreased with time in both the lonapalene- and vehicle-treated sites (Fig 1). Statistical analysis by Wilcoxon's Signed Rank Test showed that the summed scores for lonapalene treated sites were significantly lower than those for vehicle-treated sites at 14 ($P = 0.02$) and 28 ($P = 0.01$) d. Pretreatment (day 0) scores for lonapalene- and vehicle-treated sites were identical. At day 4 the mean score for lonapalene-treated sites was lower than that for vehicle-treated sites, but the difference did not reach statistical significance ($p > 0.05$). There were no significant changes in haematologic, biochemical, and urinary analyses on comparison of results obtained before and immediately after the trial.

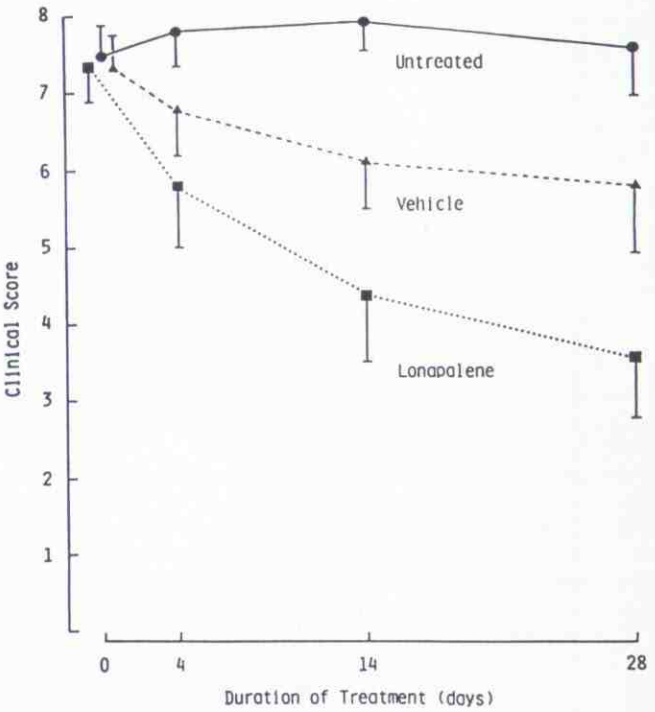

Figure 1. Summed clinical scores (mean ± SEM, n = 9) for untreated *(closed circle)*, vehicle- *(closed triangle)*, and lonapalene- *(closed square)* treated psoriatic plaques immediately before and at 4, 14, and 28 d after starting the trial.

Saturated solutions of lonapalene in HEPES-buffered MEM, when serially diluted 2 to 16 times and used as media in the agarose microdroplet assay, had no effect on the responses to 100 pg LTB_4 (Table I). Furthermore, when chamber fluid obtained from the normal volunteers who had applied 2% lonapalene ointment twice daily was purified as described, the purified residues had no inhibitory activity towards exogenously added LTB_4 in the microdroplet assay (Fig 2). These results indicated that any possible carry-over of lonapalene into the HPLC fractions analyzed would not interfere with the LTB_4 bioassay.

The recovery of exogenous LTB_4 (100 pg) added to 1 ml PBS, extracted, purified by HPLC, and quantified by the agarose microdroplet assay, as described, was 19.5 ± 2.8 pg (mean ± SEM, n = 6). The coefficient of variation in this experiment, in which the final samples were all measured in the same microdroplet assay, was 25%.

The levels of LTB_4, 12-HETE, and AA (mean ± SEM values) in chamber fluid samples are shown in Table II. There was a statistically significant reduction of LTB_4 levels in samples from lonapalene-treated sites on comparison with vehicle-treated and untreated

Table I. Effects of a Range of Dilutions of Medium Saturated with Lonapalene on Leucocyte Locomotor Responses to LTB_4 in Agarose Microdroplet Assay

Dilution of Saturated Lonapalene Solution	Chemokinetic Movement (mm) in Response to 100 pg LTB_4[a]
Twofold	0.88 ± 0.15
Fourfold	0.95 ± 0.13
Eightfold	0.90 ± 0.14
16-fold	0.86 ± 0.11
Medium without lonapalene	0.91 ± 0.13

[a] Values represent mean ± SEM of four experiments (two carried out in duplicate and two in quadruplicate).

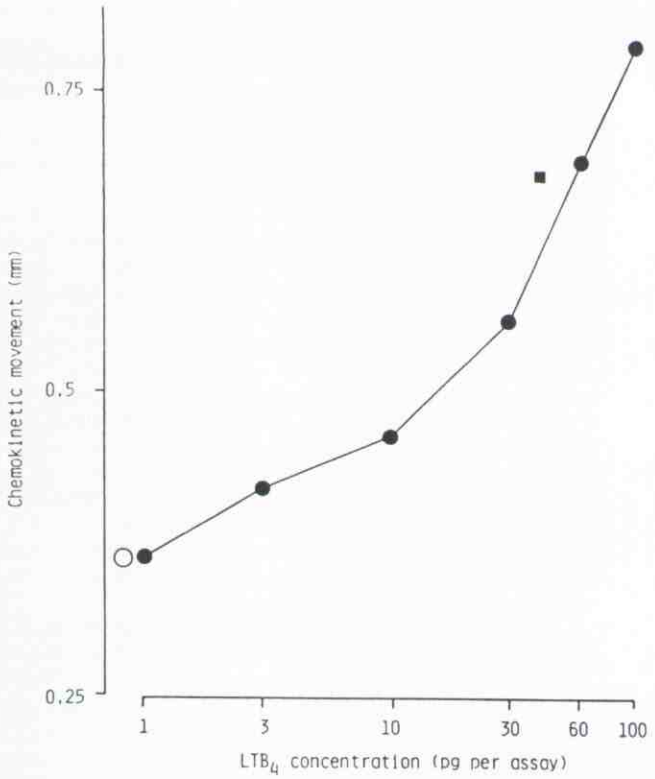

Figure 2. Effects of material in appropriate fractions after HPLC purification of chamber fluid samples from lonapalene-treated normal skin, on responses to exogenously added LTB_4 in the agarose microdroplet assay. A standard LTB_4 dose-response curve is shown, each point *(closed circle)* representing the mean of duplicate estimations. Fractions (1.5 min) coeluting with standard LTB_4 after reversed-phase HPLC of extracts of chamber fluid from lonapalene-treated normal skin were redissolved in HEPES-buffered MEM (0.3 ml) and exogenous LTB_4 added as described. Duplicate aliquots (0.1 ml) containing 60 pg exogenously added LTB_4 were tested in the same assay (*closed square*: mean result of analysis of samples from the four normal volunteers; SEM is within the margins of the symbol). Background activity in the assay is shown *(open circle)*.

sites at 4 d, and on comparison with vehicle-treated sites at 14 d. In contrast to the effects on LTB_4, there were no significant changes in the mean levels of 12-HETE and AA in samples from lonapalene treated sites at either time point.

In Table III the clinical and pharmacologic effects of lonapalene in individual patients are compared. It can be seen that reduction in the chamber fluid LTB_4 level after 14 d of lonapalene treatment was associated with a subsequent reduction in clinical score in seven out of the nine patients completing the trial.

Table III. Reduction in Chamber Fluid Levels of LTB_4 at 14 d Compared with Reduction in Clinical Score at 28 d Following Lonapalene Treatment, in Individual Patients

	LTB_4 Equivalents (pg/sample) at 14 d			Clinical Score at 28 d		
Patient Number	V[a]	L[b]	V-L[c]	V[a]	L[b]	V-L[c]
1	78	17	61	4	1.5	2.5
2	87	42	45	9	5	4
3	87	0	87	8	7	1
4[d]	81	5	76	1	1	0
5	102	53	49	8	5	3
6	26	0	26	8	6	2
7[d]	32	32	0	4.5	2	2.5
8[e]						
9	90	18	72	5	4	1
10	87	6	81	5	0.5	4.5

[a] Values for vehicle-treated sites.
[b] Values for lonapalene-treated sites.
[c] Values for lonapalene-treated sites subtracted from values for vehicle-treated sites, demonstrating additional effects of drug over vehicle alone.
[d] In patients 4 and 7, V-L for LTB_4 equivalents did not correlate with V-L for clinical score.
[e] Patient 8 withdrew from the trial, as described in *Methods*.

DISCUSSION

Previous clinical studies have demonstrated the therapeutic efficacy of topically applied lonapalene in psoriasis. Lassus and Forsstrom [27], in a double-blind comparison between 1% lonapalene gel and 0.025% fluocinolone acetonide gel, demonstrated equivalent therapeutic responses after 4 weeks of treatment, although no comparisons were made with plaques treated with vehicle alone. Jansen et al [28], in a study presented as a poster and published in abstract form, showed that 0.5% lonapalene ointment was as effective as 0.025% fluocinolone acetonide ointment, and significantly superior to vehicle alone. In their study of 19 psoriatic patients, one-third were reported to experience local irritant reactions to the lonapalene preparation.

The present clinical and pharmacologic study was limited to ten patients in view of the quantity of analytical work required. For example, quantification of LTB_4, 12-HETE, and AA, as described, involved recovery of six paired chamber fluid samples, two stage lipid extraction procedures, and a total of 18 HPLC purification steps per volunteer, prior to bioassay, derivatization, and GC-MS analysis of purified material. Nevertheless, statistically significant improvement was found when the summed scores for erythema, induration, and scaling from sites treated with 2% lonapalene ointment were compared with those from vehicle-treated lesions at 14 and 28 d (Fig 1). Figure 1 shows a mean reduction in clinical score of approximately 50% when the results for lonapalene-treated sites are compared with those for untreated sites at 28 d, an outpatient clinical response which may be potentially useful. A significant vehicle effect is also demonstrated in Fig 1. This finding highlights

Table II. Levels of LTB_4 Equivalents, 12-HETE, and AA (mean ± SEM) in 0.9-ml Chamber Fluid Samples from Untreated (U), Vehicle- (V), and Lonapalene- (L) Treated Plaques of Psoriasis

	LTB_4 Equivalents (pg/sample) n = 9			12-HETE (ng/sample)[a] n = 6			AA (ng/sample)[a] n = 6		
Days	U	V	L	U	V	L	U	V	L
4	59 ± 12	73 ± 10[b]	27 ± 11[c]	28 ± 6	30 ± 3	22 ± 5[e]	164 ± 32	191 ± 40	196 ± 56[e]
14	53 ± 17	74 ± 9[b]	19 ± 6[d]	30 ± 5	28 ± 6	23 ± 6[e]	187 ± 57	191 ± 59	123 ± 37[e]

[a] Analysis of samples from six of the nine volunteers was completed.
[b] $p > 0.05$ on comparison with untreated sites.
[c] $p = 0.01$ and 0.006 on comparison with vehicle-treated and untreated sites, respectively.
[d] $p = 0.001$ and > 0.05 on comparison with vehicle-treated and untreated sites, respectively.
[e] $p > 0.05$ on comparison with both vehicle-treated and untreated sites.

the difficulty that may be encountered in topical therapeutic trials in psoriasis. The emollient effect of greasy bases are likely to reduce lesional scores in which scaling and induration are taken into account.

Pharmacologic analysis showed a significant reduction in chamber fluid levels of LTB_4-like material from lonapalene-treated vs vehicle-treated sites at both 4 and 14 d. In contrast, the chamber fluid levels of 12-HETE and AA were not significantly affected by lonapalene treatment, findings which agree with the pharmacologic selectivity of lonapalene as demonstrated in vitro [24]. Interestingly, lonapalene was shown to elute near LTB_4 in the reversed phase HPLC purification system used prior to quantification of LTB_4 by bioassay. It was therefore necessary to show that lonapalene did not inhibit the bioassay both by in vitro (Table I) and in vivo (Fig 2) experiments. As recovery of LTB_4 in the assay system used was approximately 20%, the measured levels of LTB_4 equivalents in chamber fluid should be multiplied by a factor of about 5 to indicate actual levels.

The ability of topical lonapalene to reduce mean lesional LTB_4-like material but not 12-HETE or AA (at an early stage of treatment) (Table II) prior to the attainment of a significant therapeutic effect, as well as the demonstration that the clinical improvement in response to topical lonapalene was preceded by a reduction in LTB_4 levels in lesional samples in seven of nine volunteers (Table III) suggest that the therapeutic effect of 2% lonapalene ointment in psoriasis may be related to inhibition of LTB_4 synthesis. These results therefore support the view that 5-lipoxygenase inhibitors may be useful in the treatment of psoriasis and that LTB_4 may be a relevant mediator of part of the pathology of this disease.The local irritant properties of lonapalene may limit its therapeutic application. It is, however, likely that the clinical use of other 5-lipoxygenase inhibitors will clarify the importance of these drugs and the pathogenic role of LTB_4 in psoriasis.

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