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A double-blind study to assess the primary irritancy of flurbiprofen (local action transcutaneous) when applied to the skin of Caucasians

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Abstract

A single-centre, double-blind, single-dose study was conducted to assess the primary irritancy of a local action transcutaneous (LAT) patch preparation of flurbiprofen (Targus/TransAct LAT) when applied to the skin of 24 Caucasian volunteers. Comparisons were made of flurbiprofen LAT with non-medicated control, unperfumed moisture cream and a plain lint patch. It was found that the primary irritancy of the flurbiprofen LAT preparation was minimal. This finding, together with previous experience in Japanese subjects, suggests that skin irritancy is unlikely to be a prevalent adverse event when flurbiprofen LAT is used clinically in Caucasian patients.

Keywords: Local action transcutaneous flurbiprofen; Primary irritancy; Caucasian

Flurbiprofen is a non-steroidal anti-inflammatory drug (NSAID) belonging to the propionic acid family. It is widely used via the oral route in the treatment of pain (Stubbs et al., 1990), osteoarthritis (Grant et al., 1980) and rheumatic diseases (Smith et al., 1987). Although NSAIDs are undoubtedly extremely valuable anti-inflammatory agents, there is growing concern about their potential for undesirable side-effects, particularly upper gastrointestinal tract ulceration and bleeding and renal impairment, to which the elderly are especially susceptible. Most of the unwanted side-effects of NSAIDs are generally related to high circulating plasma concentrations (Famaey, 1985). More recently, NSAIDs have become available for local, transcutaneous administration, thus minimising plasma flurbiprofen concentrations and theoretically decreasing systemic adverse events, potentially providing a safer alternative to that of oral administration.

Local application, however, may cause adverse events specific to this route of administration, which should be addressed early in the formulation's development. This study was undertaken to assess the primary skin irritancy of a local action transcutaneous (LAT) preparation of flurbiprofen (Targus/TransAct LAT, a white adhesive patch with a peppermint-like aroma), when ap-

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plied to the skin of Caucasians. A comparison was made of the primary skin irritancy of flurbiprofen LAT with a matching non-medicated control (placebo), an unperfumed moisture cream (test standard) and a blank lint square.

Flurbiprofen LAT was supplied by Boots Pharmaceuticals, Nottingham, UK, in the form of a non-woven, polyester-backed patch (10 × 13.6 cm) supporting a formulation containing 40 mg flurbiprofen dissolved in peppermint oil and distributed uniformly in an oil water emulsion in an acrylic moisturised base. The primary irritancy of flurbiprofen LAT was evaluated in a single-centre, comparative within-volunteer, double-blind study in 24 consenting, healthy Caucasian volunteers. Volunteers were excluded from the study if they had a history of asthma, peptic ulceration, allergy to NSAIDs or significant dermatological disease.

The test product was a non-occluded, 1 cm square of flurbiprofen LAT (0.3 mg flurbiprofen). Preparation of the 1 cm^2 test product did not damage the integrity of the formulation. Reference products were (i) a matching non-medicated control (placebo) preparation, (ii) an unperfumed moisture cream on a 1 cm square of lint (test standard) and (iii) a blank 1 cm square of lint. The site to which each of the four products was applied was determined by a randomisation schedule in blocks of four, which ensured that each product was placed on each of four designated template positions an equal number of times, over the volunteer panel as a whole. A card template was used to position the four test products to the volar aspect of one forearm of each volunteer and it was held in position with hypo-allergic sticking plaster for 24 h.

Immediately prior to the application of the patch and at 25, 48 and 72 h after application of the patch (1, 24 and 48 h after removal), a trained assessor, experienced in conducting patch-test studies, assessed the skin at the patch-test site for erythema and surface damage using two separate 7-point scales (from 0 to 6). Adverse events were reported by the volunteers during and shortly after the study. All statistical tests were two-tailed and significant differences between treatments

Table 1
Summary of erythema score at 25 h after patch application, by treatment

Erythema score [a]	Flurbiprofen LAT *n*	Non-medicated control (placebo) *n*	Unperfumed moisture cream *n*	Blank lint square *n*
0	22	17	6	17
1	1	1	2	2
2	0	6	4	2
3	1	0	6	1
4	0	0	4	2
5	0	0	2	0
6	0	0	0	0
Median	0	0	2.5	0

[a] Erythema score

Score	Classification	Definition
0	no reaction	no visible reaction
1	minimal erythema	possible reaction
2	very slight erythema	definite faint redness, not obvious until located with template
3	slight erythema	easily seen slight redness, obvious before use of template
4	moderate erythema	obvious red square
5	strong erythema	strong redness
6	severe erythema or oedema	intense redness or oedema with/without redness

n = number of patients. Difference between treatments $\chi^2 = 19.49$, 3 df, $p < 0.001$ (Friedman's test).

were determined with reference to the 5% level. The Friedman's test (Hollander and Wolfe, 1973a) was used to assess whether or not the four treatments had an equal effect, and the Wilcoxon signed-rank test (Hollander and Wolfe, 1973b) was used for pairwise comparisons between flurbiprofen LAT and each of the other three treatments for erythema and surface damage.

One volunteer withdrew from the study (sore throat) and was therefore unable to provide data for the 72-h post-application assessment. Complete data were obtained for the remaining 23 volunteers. No erythema was found for 22/24 (92%), 21/24 (88%) and 20/23 (87%) of the volunteers at the flurbiprofen LAT treatment site, at the respective 25-, 48- and 72-h assessments. In only one case, after 25 h, was the severity of erythema score for the flurbiprofen LAT treatment site greater than 2 (Table 1).

At the 25-h assessment, the incidence of erythema following flurbiprofen LAT was lower than with the other treatments. Friedman's test showed an overall significant difference in erythema ($p < 0.001$) between treatments. At the 48- and 72-h assessment points there were no statistically significant overall treatment effects. Skin surface damage was reported in only 1/24 (4%) of the volunteers at the flurbiprofen LAT treatment site and this was described as 'barely visible surface wrinkling' at the 25-h assessment point. Friedman's test showed no significant treatment effects at any of the assessment points for skin surface damage.

Pairwise comparisons between flurbiprofen LAT and the other three test products showed a statistically significant difference for erythema, in favour of flurbiprofen LAT, which had a lower incidence of erythema at 25 and 48 h post-application ($p = 0.0008$ and 0.013, respectively; both values significant at 5% after adjustment for multiple comparisons) when compared with the unperfumed moisture cream. None of the other between-treatment comparisons for erythema or surface damage showed any statistically significant differences.

The 95% confidence intervals for the Hodges-Lehmann estimators supported the pairwise comparison. For example, the 95% interval for the difference in erythema at 25 h between the unperfumed moisture cream and flurbiprofen LAT supported the results of the pairwise comparison test (interval = 1.5, 3 in favour of flurbiprofen LAT). The Hodges-Lehmann estimator includes zero differences which are not considered by the Wilcoxon test.

No unexpected or severe adverse reactions occurred during the study. A total of 58 adverse events were recorded, 51 of which were minor skin reactions local to the site of application of the test products. The seven events unrelated to treatment site consisted of the following: itchy skin around the hypo-allergic sticking plaster (1), headache (2), nausea (1), sore throat (1) and marginal neutropenia (2) defined at the post-study blood screen by a neutrophil count less than 2.0×10^9/l. At some treatment sites more than one reaction was recorded. Five of 46 (11%) reactions, which were dermatological in nature, occurred at the sites at which flurbiprofen LAT was used, compared with 9/46 (20%) with non-medicated control, 18/46 (39%) with the moisture cream and 14/46 (30%) with the blank lint square. The condition of the two volunteers who had marginal neutropenia (neutrophil counts 1.7 and 1.82×10^9/l) at the post-study blood screen had resolved (2.64 and 2.04×10^9/l when the samples were repeated. It was highly unlikely that these occurrences were associated with any of the test products. Overall, the numbers of volunteers experiencing adverse events, and the number of adverse events, were lower for the flurbiprofen LAT preparation than for the other three treatments.

Studies on a topical application of flurbiprofen have been conducted in Japanese subjects and have demonstrated effective local absorption of flurbiprofen from the topical preparation (Sugawara, 1987), and efficacy (Hiranuma et al., 1982).

In a dermal safety (patch test) study in Japanese subjects, the dermal irritation index for a topical preparation of flurbiprofen was found to be low (Sugai, 1992). Because Japanese skin appears to be more sensitive to allergens and irritants than other skin types (Rapaport, 1984), it can be anticipated that the incidence of dermal

reactions to flurbiprofen LAT would be even lower in Caucasians. The low incidences of erythema and skin surface damage caused by flurbiprofen LAT in this study imply that the primary irritancy of this product, is also minimal when applied to Caucasian skin.

A conceivable criticism of this study is that it entails an acute, rather than subchronic, exposure to the test substance. This exposure is long enough to detect a positive reaction to the test standard (unperfumed moisture cream) and would appear predictive of clinical trial results. In patients exposed to flurbiprofen LAT 40 mg twice daily for up to 2 weeks the incidence of adverse events was 6% on flurbiprofen LAT and 4.9% on placebo patch, most adverse events being due to local dermal reactions (Muldoon et al., 1994).

It is concluded, therefore, that skin irritancy is unlikely to be a prevalent adverse event, when flurbiprofen LAT is used clinically in Caucasian subjects.

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