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CLINICAL FOCUS: PAIN MANAGEMENT
ORIGINAL RESEARCH

Cutaneous irritancy of an ibuprofen medicated plaster in healthy volunteers

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ABSTRACT

Objective: Ibuprofen is a commonly used non-steroidal anti-inflammatory drug administered to treat injuries, joint pain, and recurrent muscular skeletal pain. The aim of this study was to determine the cutaneous irritancy of a medicated ibuprofen plaster compared with a placebo plaster in healthy volunteers.

Methods: Healthy volunteers (N = 31) were treated at the same time with one ibuprofen and one placebo plaster. The ibuprofen and placebo plaster were applied in a randomized fashion to sites on the left or right side of subjects' lower backs. At each scheduled visit, the plasters and applications sites were assessed for degree of adhesion and skin irritancy, respectively. The plasters were applied on study Days 1, 2, 3, 5, 8, 10, 12, 15, 17, and 19, with final plaster removal on Day 22.

Results: The ibuprofen medicated plaster compared with placebo had a lower percentage of Grade 1 (23.3% vs. 46.7%, respectively), Grade 2 (10% vs. 20%), and $\geq$ Grade 3 (3% vs. 16.1%) irritancy scores after 21 days of application. The mean irritation score across the study was 0.40 for the ibuprofen medicated plaster and 1.18 for the placebo plaster. The irritation score on Day 22 of the study was 0.53 for the ibuprofen medicated plaster and 1.50 for placebo. The placebo plaster was associated with a higher number of stopped applications due to Grade 3 or above skin reactions compared with the ibuprofen medicated plaster (5 vs. 1, respectively).

Conclusion: The ibuprofen medicated plaster was well tolerated and was associated with lower irritancy than the placebo plaster.

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Ibuprofen; plaster; patch; NSAIDs; cutaneous reaction; irritancy

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are routinely used to treat injuries, joint pain, and recurrent muscular skeletal pain that may result from a number of causes including physical activity and aging [1]. Topical NSAIDs for pain relief have been available for many years and are widely used, in part because they do not require prescription, and they can manage the symptoms of injury, reduce pain, and improve mobility [2,3].

The NSAID ibuprofen is often used to treat pain associated with several conditions, such as sports-related injuries, postoperative pain, recurrent pain, and chronic arthritis [4–6]. Ibuprofen acts by blocking the production of inflammatory prostaglandins, such as PGE₂, through inhibition of the cyclooxygenase enzyme system [7]. Ibuprofen is most commonly administered orally, and consequently acts systemically to relieve pain and reduce inflammation [8]. The over-the-counter oral dose of ibuprofen is 200–400 mg, with a maximum daily dose of 1200 mg. Depending on dose, ibuprofen is at least as effective as paracetamol, ketoprofen, and aspirin in controlling pain [9].

Gel, cream, and plaster formulations of ibuprofen have been developed to avoid side effects related to oral administration of the drug, such as gastrointestinal toxicities [10–14].

The use of a topical plaster delivery systems has the benefit that therapeutic drug concentrations can be achieved for extended periods of time in the target tissues and muscles to reduce inflammation and pain but results in low systemic concentrations of the drug compared with oral administration [14]. Studies have found that topical application of NSAIDs have superior safety profiles and are associated with fewer adverse events (AEs) compared with orally administered drug [10,15,16]. Most AEs associated with medicated plaster administration of NSAIDs are cutaneous in nature, and gastrointestinal AEs are rare [15].

A once-daily locally applied ibuprofen 200-mg medicated plaster has been developed for the treatment of nonserious localized pain. The plaster is a new formulation of the drug supported on a flexible platform. A plaster formulation has several advantages compared with gel formulations which may increase patient compliance, including convenience and ease of application [17,18]. Gel formulations can be difficult to apply and require reapplication up to three times per day. Two Phase 3 studies have found that the ibuprofen-medicated plaster results in rapid and clinically relevant reduction of pain in patients with blunt musculoskeletal injuries or

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recurrent pain (unpublished results). In addition, pharmacokinetic analysis indicated that the systemic absorption of ibuprofen from the plaster was low compared to regular oral dosing and that the levels of the drug leaving the plaster over a 24-h period are consistent with amounts required for therapeutic relief (unpublished results). This study was carried out to assess the safety of the ibuprofen medicated plaster by evaluating the cumulative irritancy potential of this new formulation.

2. Material and methods

This double-blind, placebo-controlled study (EudraCT: 2009-018061-12) was conducted in accordance with the Declaration of Helsinki and complied with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements. The study protocol was reviewed and approved by the Reading Independent Ethics Committee. All patients gave their written informed consent.

2.1. Study population

The study included healthy adults (≥ 18 years of age) with no significant illness or skin disease. Subjects receiving any medication (e.g. corticosteroids) up to 3 days prior to study start which could interfere with the study were excluded. There was not concomitant use of antihistamines during the trial period. Also excluded were subjects with any previous history of allergy or hypersensitivity to any of the drugs or formulation constituents, which in the Investigator's opinion, might have precluded the use of an NSAID. The drug hypersensitivity included aspirin-sensitive asthma or a previous allergic response to a NSAID, including bronchospasm, urticaria, angioedema, and rhinitis. Subjects with a positive history of drug or alcohol abuse within the year preceding the study or a history of psychotic illness, attempted suicide, or neurosis were also excluded. Subjects were ineligible if they had participated in a clinical study in the 30 days preceding the start of the current trial. Subjects could be withdrawn from the study for violation of the study protocol, if the subject declined further participation, or if in the judgment of the Investigator it was in the best interest of the subject,

2.2. Study design

The cumulative irritancy potential of a 4 cm x 4 cm piece cut from of a 14 cm x 10 cm 200-mg plaster was evaluated using an adaptation of the Shelanski repeat insult plaster test methodology [19]. This test was chosen as it is a well-documented, recognized, and established methodology. The placebo plaster contained the same matrix as the study product.

Every subject received two plasters at each timepoint: an ibuprofen (containing 23 mg of drug) and a placebo (control) plaster. Each plaster was applied separately to the skin on the lower part of the back between the iliac and the midpoint between the iliac and the shoulders; one plaster was applied on the left and the other on the right side of the body (as per randomization schedule). The area over the vertebral column was avoided. The plasters were applied under a breathable

Tegaderm dressing to ensure plasters stayed in contact with the skin. The plaster size used in the study was selected to match the size of the Tegaderm dressing and to allow sufficient clearance between the plaster sites. The test plasters were applied in a manner to avoid covering any features such as moles or blemishes. The test sites were not specially cleaned prior to application.

Subjects were randomized and baseline values were collected on Day 1. The plasters were applied on study Days 1, 2, 3, 5, 8, 10, 12, 15, 17, and 19, with final plaster removal on study Day 22. Assessment of the skin under the plaster occurred on Days 2, 3, 5, 8, 10, 12, 15, 17, 19, and 22. The skin beneath the applied plaster was assessed for tolerance each time the prior visit plaster was removed and a new one applied. Plasters were in constant contact with the skin for 22 days except for the brief time (minutes) when the plaster was removed, the site was clinically assessed, and a new plaster was applied. The maximum dose of ibuprofen a subject was exposed to was approximately 230 mg over the 22-day period. Safety was monitored throughout the study. In the case of a Grade 2 dermal response, the decision to reapply the plaster was determined by an experienced trained dermal assessor(s). In all circumstances, Grade 3 or above dermal reactions resulted no reapplication of the plaster.

Assessments included plaster adhesion and tolerance, including dermal response, other effects, and burning or stinging (as detailed below). The adhesion of the plaster was recorded prior to removal at each visit, using a five-point ranking scale ($\geq 90\%$ adhered, essentially no lift from the skin of the adhesive plaster; 75% to $<90\%$ adhered, some edges lifting off the skin but the plaster was not significantly affected; 50% to $<75\%$ adhered, up to half detached and the plaster was significantly affected; $<50\%$, more than 50% detached; plaster completely detached).

For assessment of tolerance, the plasters were carefully removed and the test site areas wiped with damp gauze swab. The sites were assessed 10 to 30 min following plaster removal, which allowed any skin reaction due to removal of the plaster to subside. All tolerance assessments were performed by a trained dermal assessor(s). Dermal response was ranked using an eight-point irritation score (0, no evidence of irritation; 1 minimal erythema which was barely perceptible; 2, definite erythema, minimal edema or minimal papular response; 3, erythema and papules; 4, definite edema; 5, erythema, edema, and papules; 6, vesicular eruption; 7, strong reaction spreading beyond test sites). Other effects were also evaluated and given letter identification (A, slight, glazed appearance; B, marked glazing; C, glazing with peeling and cracking; F, glazing with fissures; G, film of dried serous exudate covering part or all the plaster site; H, small petechial erosions and/or scabs). Subjects were also asked by the trained dermal assessor whether they experienced any burning or stinging at the study test site. No assessment of efficacy was made during the study. Treatment compliance was evaluated by the number of plasters that had completely detached prior to the subject's return visit.

Since the dosage regimen was fixed, subjects who returned to the study with the plaster attached were considered to have

full exposure. If the plaster had become completely detached, the subject was deemed to have had partial exposure. Subjects who were not replastered due to product reactions were included up until the time they were stopped. Subjects who were instructed to remove the plaster between study visits for safety reasons were classified as having full exposure.

The primary endpoint in terms of safety evaluation for this irritancy study was the skin reaction (mean irritancy scores at each of the 10 skin assessments). AEs were evaluated throughout the study.

Safety was assessed throughout the study. The Investigator classified AEs by severity and relationship to study drug. Mild AEs were defined as those events that did not limit usual activities but the subject may experience slight discomfort. Moderate AEs resulted in some limitation of usual activities, and the subject experienced significant discomfort. Severe AEs result in an inability to carry out usual activities, and the subject may experience intolerable discomfort or pain.

2.3. Randomization and masking

Drug supplies were randomized using a computer-generated randomization schedule provided by the Sponsor. On entry to the study, subjects were allocated a unique subject number in numerical sequence. Application site was randomized according to a preprepared randomization code which ensured random positioning of the ibuprofen and placebo plaster to either the left or right side of the back. Once randomized, the positions of the ibuprofen and placebo plasters remained unchanged for all subsequent applications. Assessments were made by a trained blinded dermal assessor (blind to product application).

2.4. Statistical analysis

No statistical power calculations for the sample size chosen were performed. The sample size (30 subjects) was selected based on FDA guidelines for the testing of medicated plaster technologies [20]. All subjects who received at least one dose of study medication were included in the safety analysis. Outcomes, including the cumulative irritation score, were presented descriptively (mean, standard deviation). Safety parameters were assessed by calculating the individual cumulative irritation score for each subject as the sum of their scores up to and including the Day 22 assessment. If observations were missing, the last observation of the subject was carried forward. If a Grade 2 or greater reaction was recorded and application of the test product was stopped, then the last observation was carried forward for all subsequent time points. One subject was unable to attend Day 15 but attended all other visits; the values for the visit prior to the missed visit were used in the analysis.

3. Results

3.1. Patient disposition and demographics

Forty subjects were screened and 31 were randomized to treatment (Figure 1). A single patient withdrew from the study on Day 17 due to a reason unrelated to the study. All timepoints for this subject, including Day 17, were included in the analysis.

Figure 1. Subject disposition. A single patient withdrew from the study on Day 17. All timepoints for this subject including Day 17 were included in the analysis^a.

Table 1. Subject demographics.

Variable	Subjects (N = 31)
Mean age, years (SD)	37.0 (13.0)
Female, n (%)	27 (87%)
Ethnic origin, n (%)	
Caucasian	30 (97%)
Other	1 (3%)

SD: standard deviation.

The study population was mostly female and Caucasian (Table 1). The mean age was 37 years. Treatment compliance was approximately 99%; six plasters detached during the study from a total of 564 applied plasters. Detached plasters during the study were due to lack of adhesion.

3.2 Assessment of irritancy

For both the ibuprofen and placebo plasters, the mean irritation score was small indicating only low levels of erythema, edema, or papules were observed (Figure 2). The mean irritation score at Day 22 for all 30 subjects who completed the study was 0.53 for the ibuprofen-medicated plaster and 1.50 for the placebo plaster (Table 2). The maximum irritation score observed with the ibuprofen-medicated plaster was three and for the placebo plaster was six. The mean irritation score across all visits was 0.40 for the ibuprofen-medicated plaster and 1.18 for the placebo plaster. Following 21 days of application, no irritancy reaction (Grade 0) to the ibuprofen-medicated plaster and the placebo plaster was observed in 63.3 and 16.7% of sites, respectively. A minority of ibuprofen-medicated plaster application sites (23.3%) and almost half of the placebo plaster application sites (46.7%) were assessed as having an irritancy of Grade 1. The presence of burning or stinging at the ibuprofen-medicated plaster application site was experienced by two subjects and at the placebo plaster application site by one subject.

Most subjects had full exposure (i.e. the plaster remained attached from visit to visit) across the 22-day study to ibuprofen (range, 90.0% to 100%) and placebo (74.2% to 100%).

During the study, 10 subjects had the application of one of the two plasters stopped; three subjects had application of the ibuprofen-medicated plaster stopped and seven had the

Figure 2. Summary of mean irritation score for ibuprofen medicated plaster and placebo plaster.

Table 2. Summary of irritancy assessment.

	Ibuprofen <i>n</i> = 31	Placebo <i>n</i> = 31
Overall mean irritation score	0.4	1.18
Day 22 mean irritation score	0.533	1.50
Maximum irritation score	3	6
Day 22 irritancy score, <i>n</i> (%)	19 (63.3)	5 (16.6)
Grade 0 (No irritancy reaction)		
Grade 1	7 (23.3)	14 (46.7)
Grade 2	3 (10)	6 (20)
≥Grade 3	1 (3.0)	5 (16.1)

placebo plaster stopped. Of the subjects that had the ibuprofen-medicated plaster stopped, one subject presented with Grade 3 skin reaction, while the other two were stopped by the blinded assessor as permitted by the protocol for Grade 2 or lower reactions. Of the seven subjects who had the placebo plaster stopped, three subjects had Grade 3 skin reactions, one had a Grade 4 skin reaction, and one a Grade 6 skin reaction, while the remaining two were stopped by the blinded assessor as permitted by the protocol.

3.3. Adverse events

A total of 27 AEs in 15 (48.4%) subjects were observed during the study. All AEs were mild (88.9%) or moderate (11.1%) in severity. Thirteen AEs were related to treatment; one with the ibuprofen-medicated plaster, six with the placebo plaster, and six that were not plaster specific. As discussed above, the ibuprofen-medicated plaster was associated with one Grade 3 skin reaction and the placebo plaster with five Grade 3 and above reactions that were considered definitely related to treatment; all were mild in severity. Six AEs were thought to be probably/possibly related to treatment and included itching over the back in one subject, erythema in two subjects, and three reports of a papular rash in one subject.

One subject withdrew from the study due to a non-plaster site specific AE of erythema. The subject developed a mild acute allergic type reaction that involved macular papular rash of the entire back, legs, and chest. The plasters were stopped and the subject recovered without sequelae. The AE was of moderate severity and was determined by the Investigator to be possibly related to treatment, although it was thought likely due to the Tegaderm. A second subject developed some rash 2 days after study removal of the last plaster that

increased over time until it involved the arms, legs, shoulders, trunk, and face of the subject. The reaction was considered a moderate AE, and the subject was treated for the skin reaction with steroids and clobetasol (Dermovate) ointment, which resulted in resolution of the rash over 2 weeks such that it was limited to a mild papular rash on the lower back. The subject was subsequently lost to follow-up.

4. Discussion

Medicated plaster drug delivery systems are increasingly being used over oral formulations due to several advantages, including convenience and increased patient compliance [17]. In addition, medicated plaster avoids systemic exposure, first-pass metabolism, and fluctuating plasma concentrations [17]. An ibuprofen 200-mg plaster offering 24-h drug exposure has been developed and has shown effectiveness in treating pain in patients with blunt musculoskeletal injuries [1]. Effective pain relief was achieved at doses much lower than those required with oral dosing (Under review) [PK manuscript].

The objective the study described here was to evaluate the cumulative irritancy potential of the plaster compared with placebo in health volunteers. The study found that the ibuprofen-medicated plaster was well tolerated and that 63.3% of subjects showed no irritancy and only 23.3% had Grade 1 skin reactions after 21 days of plaster application. It is well documented that ibuprofen can cause both acute allergic type reactions and delayed (type 4) hypersensitivity reaction and anaphylactic reactions in susceptible individuals (at least 1% of exposed individuals) [21–23]. Therefore, the hypersensitivity events seen in this study were not unexpected. Ibuprofen plaster has previously displayed a significant superior efficacy in clinical trials over placebo for orally treatment [1]. The side effects manifested in the placebo patch in this study were not treated. In contrast, an Ibuprofen plaster has the benefit of providing prophylactic COX 1 and COX 2 inhibition for any possible irritation from the adhesive. Therefore, the manifestation of irritancy symptoms is controlled in the ibuprofen arm of the study.

The skin reactions observed in this study are consistent with those observed for other transdermal therapeutic systems [17]. Prior studies have observed that irritant contact dermatitis is the most common type of application-site reaction and often

consists of erythema with itching of burning, and sometimes accompanied by edema [24]. Consistent with the current study results, these skin reactions typically are mild to moderate in severity, transient in nature, and occur in 20–50% of patients [24]. Signs and symptoms of irritant contact dermatitis may be minimized through rotation of the application site, careful removal of the plaster, the use of moisturizers, and topical corticosteroids if necessary [24,25]. Allergic contact dermatitis can also occur, but is relatively rare [17].

5. Conclusions

The new ibuprofen-medicated plaster was associated with low irritancy and in fact was lower than that of the placebo plaster in healthy volunteers.

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Declaration of interest

M Maganji and A Bhatt are employees of Reckitt Benckiser. MP Connolly is a consultant for Reckitt Benckiser. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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