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CLINICAL FEATURE
ORIGINAL RESEARCH

Cutaneous irritancy of an ibuprofen medicated plaster in healthy volunteers

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ABSTRACT

Objectives: To assess the irritation and contact sensitization potential of a 200 mg ibuprofen medicated plaster.

Methods: This double-blind, phase-1 placebo controlled study had two phases; the induction phase to evaluate the irritant potential of continuous application of the plaster, and the challenge phase to assess contact sensitivity (allergy). The cumulative irritancy potential was evaluated using an adaptation of the Shelanski method. Healthy adults (≥ 18 years of age) ($N = 210$) were treated simultaneously with one ibuprofen medicated and one placebo plaster applied in a randomized fashion to either the left or right side of the lower back. During the induction phase, plasters were applied on Days 1, 3, 5, 8, 10, 12, 15, 17, and 19 and the final plaster removed on Day 22. At each scheduled visit plasters and applications sites were assessed for degree of adhesion and skin irritation (score of 1 = no irritation to 7 = strong reaction spreading beyond test sites), respectively. The challenge phase followed a two-week washout period. A plaster was applied on Day 36 for 48 h and assessment occurred on Days 38, 39, and 40.

Results: The mean cumulative irritation score during the induction phase was lower for the ibuprofen medicated plaster than the placebo plaster (0.32 vs. 1.23, respectively). Three (1.4%) subjects experience a dermal reaction of grade ≥ 3 for the ibuprofen medicated plaster compared with 27 (12.7%) for the placebo plaster. Following challenge with ibuprofen or placebo plasters, 12 subjects (6.2%) with the ibuprofen medicated plaster and four (2.2%) with the placebo plaster had skin reaction of assessment grade higher than the induction phase. One subject for the ibuprofen and two for the placebo plaster had reactions with grade > 2 . No subjects showed an increase in sensitization on Day 39 or 40 compared with Day 38.

Conclusions: The findings indicate that the both the irritancy and contact sensitization of the ibuprofen medicated plaster is acceptable.

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Ibuprofen; allergy; sensitization; irritant; plaster; patch; pain

1. Introduction

Nonserious joint or recurrent muscular skeletal pain is commonly treated with topical non-steroid anti-inflammatory drugs (NSAIDs) [1]. Ibuprofen is an NSAID that is widely used to treat soft-tissue pain, postoperative pain, and chronic pain due to a number of diseases such as rheumatoid arthritis and ankylosing spondylitis [2,3]. Ibuprofen reduces pain by inhibiting the cyclooxygenase enzyme system resulting in reduction in the synthesis of prostaglandins [4]. Ibuprofen, like other NSAID, has the advantage that it is an over-the-counter medication and hence does not require a prescription [5–9].

Ibuprofen is most often administered orally, and consequently acts systemically to reduce pain and inflammation [10]. Oral administration of ibuprofen is associated with a number of adverse side effects with the most common being related to the gastrointestinal tract, kidneys, and the coagulation system [10–12]. However, gel, cream, and plaster formulations of NSAIDs have been developed to avoid side effects associated with systemic administration of the drug,

particularly gastrointestinal-related toxicities [13–15]. Gel formulations of NSAIDs, including ibuprofen, are associated with fewer adverse events (AEs), most of which are mild skin reactions at the site of application [13–15]. For example, the incidence of gastrointestinal AEs with topically applied NSAIDs are $< 1\%$ compared with 15% for oral NSAIDs [13,15]. Gel formulations can be limited by being cumbersome to apply and the dosing can vary due to inconsistency in the application of the gel. In addition, the ibuprofen gel formulation needs to be applied three times per day.

An ibuprofen-medicated plaster has been developed as an over-the-counter therapy for nonserious localized pain. The ibuprofen-medicated plaster has the advantage that it is applied once a day and is easier to apply than the gel formulation. Pharmacokinetic analysis indicated that the systemic absorption of ibuprofen from the medicated plaster was low compared with regular oral dosing and that the levels of the drug leaving the plaster over a 24-hour period were consistent with amounts required for therapeutic relief (Lewis personal

communications). In addition, the ibuprofen-medicated plaster has been found in a Phase 3 study to clinically significantly reduce pain in subjects with blunt musculoskeletal injuries [16].

Only a limited number of studies have specifically evaluated the irritant potential and/or sensitivity/allergy to topically applied ibuprofen in humans [17–19]. The purpose of the study was to evaluate the skin irritancy and the contact sensitivity potential of the ibuprofen-medicated plaster.

2. Methods

Ibuprofen plasters were formulated, using the racemic product, with the active and excipients selected to be suitable for topical administration. Ibuprofen has a well-documented use in topical products such as gels and has been shown to be at most mildly irritating to ocular mucosa but not to cause contact sensitization or phototoxicity. Similarly, the excipients have a long history of use and an established safety profile and were chosen because they have shown lack of or low potential for dermal irritation, ocular irritation, contact sensitization, or phototoxicity in preclinical studies and available literature-based evidence.

The study was a prospective double-blind placebo-controlled trial that was performed in accordance with ICH Good Clinical Practice and the ethical principles contained within the Declaration of Helsinki. The study protocol was approved by South East Wales Research Ethics Committee and all participants gave their written informed consent. The study was designed to investigate the tolerance of the ibuprofen-medicated plaster relative to the placebo control and development of sensitivity (allergy) to the plaster. The study included 3 weeks of repeated induction exposure which was followed by a 2-week rest period and then followed by a 48-h challenge to elicit the sensitization response. No assessments of efficacy were made during the study.

2.1. Study population

Healthy adults (≥ 18 years of age) with no significant concurrent illness or skin disease were eligible for the study. Subjects receiving any treatment or medication that may interfere with the study (e.g. corticosteroids) up to 3 days prior to study start were excluded. Subjects with a history of psychotic illness, attempted suicide, or neurosis were also excluded. Subjects were ineligible for the study if they had a history of drug or alcohol abuse within the past year. Also excluded were subjects with any previous history of allergy or known intolerance to any of the drugs or formulation constituents, which might have precluded the use of an NSAID, including aspirin-sensitive asthma, bronchospasm, urticaria, angioedema, and rhinitis. Subjects were ineligible if they had participated in a clinical study in the prior 30 days. A subject could be withdrawn from the study at any time due to AEs that the Investigator believed may cause severe or permanent harm, violation of the study protocol, the Investigator felt it was in the best interest of the subject, or the subject declined further study participation.

2.2. Study design

Drug supplies were randomized using a computer-generated randomization schedule provided by the Sponsor. On entry, subjects were allocated a unique subject number in numerical sequence, which ensured random allocation of active and placebo patches to test sites on the back. The Sponsor held the master code for the randomization schedule and supplied the Investigator the randomization code for each subject. Once randomized, active and placebo patch positions (left or right) remained unchanged for all subsequent patch applications. The blind of the study was maintained by staff dedicated to dispensing and application of the study products who had no involvement in study assessments or evaluation of the causality of AEs. Throughout the study, subjects, investigators, and aspect dermal assessors remained blinded. The blind was not broken during the study.

For assessment of patch adhesion and skin assessment, staff were trained at the start of the study and prior to any activities to ensure consistency between staff. The study was conducted at Aspect Clinical, Vine House, New Street, Ledbury, Herefordshire, HR8 2DX, U.K. First subject enrolled on 19 July 2010 and last subject completed on 1 November 2010.

2.2.1. Evaluation of irritant potential

The cumulative irritancy potential of a 4 cm $\times$ 4 cm piece cut from a 14 cm $\times$ 10 cm 200-mg ibuprofen medicated plaster was evaluated by an adaption of the repeat insult plaster test methodology of Shelanski [20], which is a previously applied methodology. Subjects were administered one ibuprofen (test) and one placebo plaster, both of which were applied to the lower part of the back between the iliac and the midpoint between the iliac crest and shoulder. The placebo plaster contained the same matrix as the study product. One plaster was applied to the left and the other to the right side of the lower back. The positioning of the test and placebo plasters on either the left or the right side of the back was randomized. Once randomized, the position of the test and placebo plaster remained unchanged for all subsequent plaster applications. The first plasters were applied on Day 1 and on Days 3, 5, 8, 10, 12, 15, 17, and 19 the plasters were removed, the test sites evaluated, and new plasters reapplied to the same sites. The plasters were applied under a breathable Tegaderm dressing to ensure the products stayed in contact with the skin. The ninth plaster was removed on Day 22. The test sites were not specially cleaned prior to plaster application. The plaster application avoided covering features such as moles or blemishes. At each dose administration time-point, subjects were exposed to about 23 mg of ibuprofen. The plaster size, and hence the dose, was selected to match the size of the Tegaderm dressing and to allow sufficient clearance between the plaster sites.

2.2.2. Evaluation of sensitization to the ibuprofen-medicated plaster

Following a 2-week washout period which started on Day 22, a challenge phase was performed to evaluate drug sensitivity (allergy) on subsequent use of the plaster. On Day 36, plasters were applied to new sites on the upper arm for 48 h. The test

site for the sensitization challenge was the outer aspect of the upper arm. One plaster was applied to the left arm and one to the right arm at a midpoint. The allocation of the ibuprofen and placebo plasters to the test sites was the same as for the irritancy assessment phase of the study.

Concomitant therapies were defined as prescribed medications, physical therapy, and over-the-counter preparations, including herbal preparations licensed for medicinal use, other than study medication and supplementary medication that the subject received during the study. The use of oral/topical NSAIDs were prohibited during the study. Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors could be used if the subject had maintained a stable dose for 4 weeks prior to Visit 1 and remained on the stable dose during the study.

2.3. Study assessments

Assessments during the induction phase of the study included plaster adhesion and tolerance. Prior to removal of the plaster at each visit, the adhesion of the plaster was evaluated using a 5-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). Tolerance was evaluated following careful removal of the plaster and swabbing of the test site with a damp gauze. The sites were assessed after ≥ 10 min by a trained dermal assessor on Days 3, 5, 8, 10, 12, 15, 17, 19, 22, and 38. Dermal response was ranked using an 8-point dermal response 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). The dermal assessor evaluated other test site effects attributed to the plaster which were 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 assessor whether they experienced any burning or stinging at the study test site. On Days 39 and 40, the subject did not have plasters to remove, but the sites were evaluated using the same criteria as described above.

During the challenge phase, contact sensitization was suspected if the skin reaction challenge was significantly greater than that observed during the early stages of induction, particularly if it occurred at both challenge sites and/or increased in severity between the first and second skin assessments following the challenge application.

Safety was evaluated throughout the study. The decision to apply a new plaster was determined by the dermal assessor in the case of Grade 2 dermal response. The application of new plaster was stopped if the dermal response was Grade 3 or higher.

2.4. Statistical analysis

No statistical justification of sample size was performed. The sample size was selected based on Federal Drug Administration (FDA) guidelines (1992) for the testing of topical and transdermal plasters [21]. This study was primarily concerned with safety evaluations and no assessments of efficacy were undertaken. The study design and approach was based on contemporaneous FDA guidance (Guidance for Industry – Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products, see <https://www.fda.gov/ohrms/dockets/98fr/990236Gd.pdf>, specifically see Section II Study Design, Part A) which does not require any such statistical analyses to be performed. Outcomes were presented descriptively. If observations were missed during the induction phase, the last observation for the subject was carried forward. If a Grade 2 or greater reaction was recorded and application of the test products stopped, then this last observation was carried forward for all subsequent time-points.

3. Results

3.1. Subject demographics and disposition

Of the 211 subjects randomized, 210 were administered on Day 1 an ibuprofen-medicated plaster and a placebo plaster. During the induction phase, ibuprofen treatment was discontinued for 6 subjects and placebo treatment for 31 subjects due to skin reactions (Figure 1). One subject was not challenged with the ibuprofen-medicated plaster and 11 were not challenged with the placebo plaster due to having skin reactions in the induction phase which was deemed not appropriate to challenges. Two subjects were withdrawn from the study due to AEs. One subject experienced a serious AE of a tendon rupture to the right hand, which was not considered related to study treatment. The other subject had nausea, which was considered possibly related to study treatment. Both AEs were judged to be moderate in severity. For the ibuprofen and placebo plaster therapies, 194 and 184 subjects, respectively, completed the entire study.

Subjects were predominately female (80%), Caucasian, and the mean age was 38.6 years (Table 1). Of concomitant medications taken during the study, antibiotics were the most common (4.7%).

3.2. Irritation analysis for the induction and challenge phases

Across the induction phase of the study, the placebo plaster was associated with higher mean irritancy score compared with the ibuprofen-medicated plaster (Figure 2). The irritancy score did not markedly vary for either the placebo or ibuprofen-medicated plasters from Days 3 through 22; the mean irritancy score for the placebo and ibuprofen-medicated plasters on Day 3 were 1.0 and 0.29, respectively, and on Day 22 were 1.38 and 0.42, respectively. During the challenge phase of the study, in which no plaster was administered on Days 38, 39, and 40, the irritancy score was less than the induction phase scores for both plasters (Figure 2). In addition, the

Figure 1. Disposition of subjects.

Table 1. Subject demographics.

Variable	Subjects (N = 211)
Mean age, yrs. (SD)	38.6 (14.1)
Female, n (%)	168 (80%)
Race, n (%)	
Caucasian	210 (99.5%)
Asian	0
Afro-Caribbean	0
Other	1 (0.5%)
Height, m (SD)	1.9 (0.09)
Weight, kg (SD)	75.0 (15.9)

SD: standard deviation.

mean irritation score reduced day on day for each of the three challenge days for both the placebo plaster and the ibuprofen-mediated plaster. The average of means cumulative irritation score for the induction phase for the placebo plaster was 1.23 and for the ibuprofen-mediated plaster was 0.32. The average of means cumulative irritation score during the challenge phase was 0.36 for the placebo plaster and 0.14 for

Figure 2. Summary of mean ibuprofen mediated plaster and placebo plaster irritation score at each visit.

the ibuprofen-mediated plaster. The number of subjects with no irritation was higher for ibuprofen than placebo at each day assessed. For example, on Day 22, 70.3 and 32% of

subjects reported no irritation for the ibuprofen-medicated plaster and placebo plaster, respectively.

The presence of burning or stinging was low (≤ 3 subjects/day) for both plasters during the induction and challenge phases of the study.

Following removal of the challenge plasters on Day 38, on 16 occasions (12 [6.2%] for ibuprofen-medicated plaster and 4 [2.2%] for placebo) the irritation scores were higher than the highest scores recorded by the same subjects during the induction period. Most subjects (10/12 for ibuprofen plaster and who reported an increase in irritancy score associated with the plaster on Day 38) had an increase of only one grade (e.g. from zero during the induction phase to Grade 1 during the challenge phase), indicating the risk of sensitization was low for the ibuprofen plaster. On Day 39, nine (7 [3.6%] for ibuprofen and 2 [1.1%] for placebo) and on Day 40, four ([2.1%] all ibuprofen) higher scores were observed than during the induction phase. One subject had an assessed Grade 7 for irritancy for both the ibuprofen-medicated plaster and the placebo plaster, suggesting the increased irritancy was due to the matrix of the plaster or the Tegaderm used to hold the plaster in place rather than the test products themselves.

3.3. Exposure

Most subjects had full exposure to the ibuprofen-medicated plaster and placebo plaster during the induction phase and the challenge phase of the study: the range of subjects with full exposure during the induction phase was 91.9–100% for ibuprofen-medicated plaster and 93.8–100% for placebo. The percentage of subjects with full exposure during the challenge phase was 99.0% for ibuprofen-medicated plaster and 98.9% for placebo.

3.4. Adverse events

A total of 198 AEs were recorded during the study, with 64% of subjects experiencing at least one AE. The most frequently reported events were upper respiratory tract infections ($n = 59$) and headaches ($n = 36$). Most AEs (98.0%; 194/198) were mild in severity and the majority (77.8%; 154/198) were not judged to be related to treatment. Five AEs were considered related to ibuprofen-medicated plaster, 29 were thought to be related to the placebo plaster, and 10 were not site-specific making it not possible to determine which plaster may have caused the event. The most common AE considered definitely related to the ibuprofen or placebo plasters were skin reactions ($n = 33$) which were mild in severity (Table 2).

As described above, one subject had a serious AE of a ruptured tendon that was not considered related to treatment. Two subjects had significant AEs. One subject experienced, during the 2-week washout period, a papular rash on her trunk for only the first day, which may have started from the plaster on the left side of her back. The subject was not exposed to the challenge plasters. The rash resolved over a 2-month period without treatment. The Investigator considered the skin reaction probably related to treatment. The other subject, on her first dermal assessment during the induction phase of the study, scored a Grade 4 at both the

Table 2. Summary of adverse events with a possible, probably or definite relationship to study treatments.

Adverse event	Number of events	Severity	Relationship
Skin reaction ($\geq$ Grade 3)	33	Mild	Definite
Aphthous mouth ulcer/ulcers	2	Mild	Possible
Pruritus beneath plaster	1	Mild	Definite
Nausea	1	Moderate	Possible
Papular rash on trunk	1	Mild	Probable
Maculopapular rash right leg	1	Mild	Possible
Pruritis of arms, legs, head	1	Mild	Possible
Perfume-like taste in mouth	1	Mild	Possible
Heartburn	1	Mild	Possible
Very dry lips	1	Mild	Possible
Migraine	1	Mild	Possible

ibuprofen and placebo plaster sites, and consequently treatment was discontinued. During the challenge phase, at the first dermal assessment, the subject scored a Grade 7 (strong erythema, edema, and papules) and both sites were itchy. The fact that Grade 4 dermal AE occurred at both the ibuprofen and placebo plaster sites indicates it was likely due to sensitivity to the components of the matrix and/or adhesive and was not due to ibuprofen. The subject was prescribed chlorphenamine 4 mg for 3 days, and the skin reaction resolved and did not return for the rest of the study. The Investigator considered the reaction definitely related to therapy.

4. Discussion

The purpose of this study was to assess the tolerance of subjects for a new ibuprofen-medicated plaster. The study had two phases; during the induction phase, the irritancy of continuous application of the plaster was evaluated and during the challenge phase the sensitivity (allergy) of subjects to the plaster was assessed. The cumulative irritation score during the induction phase for the ibuprofen-medicated plaster was lower than that of the placebo plaster. Three (1.4%) subjects experienced a dermal reaction of Grade ≥ 3 for the ibuprofen-medicated plaster compared with 27 (12.7%) for the placebo plaster. More subjects were not challenged with the placebo plaster ($n = 11$) compared with the ibuprofen-medicated plaster ($n = 1$) since having a skin reaction in the induction phase was considered inappropriate to challenge. Following challenge with ibuprofen-medicated plaster or placebo plaster, 12 subjects (6.2%) with the ibuprofen-medicated plaster and 4 subjects (2.2%) with the placebo plaster had skin reaction of assessment grade higher than the induction phase. All but one of these subjects for the ibuprofen-medicated plaster and all but two for the placebo plaster had grade ≤ 2 reactions, suggesting that both plasters had low contact sensitization potential. No subjects showed an increase in sensitization on Day 39 or 40 compared with Day 38. The lower irritancy seen with the ibuprofen-medicated plaster compared with placebo suggests that the observed irritancy was due to the matrix and/or adhesive, and this irritancy was mitigated by the presence of ibuprofen. The results described here are consistent with a previous pilot study involving a much smaller trial population [19].

The most common AE considered definitely related to the ibuprofen or placebo plasters was mild skin reactions ($n = 33$).

This finding is consistent with other transdermal therapeutic systems, which found that common application site reactions are typically mild to moderate in severity and include erythema with itching and burning and sometimes edema [22]. In the current study, the presence of burning or stinging during both the induction and challenge phase of the study was ≤ 3 subjects/day.

In two cases, a suspected hypersensitivity reaction took place, one was a generalized reaction following the induction phase and one was a sensitivity reaction during the challenge phase. The sensitivity reaction was likely due to the plaster adhesive matrix as the subject reacted to both test and placebo plasters.

The findings of the study reported here are consistent with a smaller study of similar design that evaluated the irritancy of the ibuprofen-medicated plaster. In the pilot study, healthy volunteers ($N = 31$) were also treated at the same time with an ibuprofen and a placebo plaster applied in a randomized fashion to the lower back [19]. Like the study reported here, the smaller study found that the ibuprofen-medicated plaster was associated with less irritancy than the placebo plaster; 63 and 16.6% showed no irritancy, respectively, and 87 and 46.7% had Grade 1 or less skin reactions after 21 days of application. The irritation score on Day 22 of the study was 0.53 for the ibuprofen-medicated plaster and 1.50 for the placebo plaster. In addition, the placebo plaster was associated with a higher number of stopped applications due to Grade 3 or higher skin reactions. The current study reported here differs from the prior study, as the current study is much larger ($n = 210$ vs. $n = 15$) in size and evaluated hypersensitivity of the ibuprofen-medicated patch, an important safety concern regarding topical application of a drug.

The low contact sensitivity observed with the ibuprofen-medicated plaster is also consistent with a prior study that evaluated delayed contact hypersensitivity of several NSAIDs [17]. Gniazdowska et al. (1999) administered plaster tests to 371 consecutive subjects with a series of NSAIDs, including acetylsalicylic acid, buprenorphine, diclofenac, etofenamate, felbinac, flufenamic acid, ibuprofen, indomethacin, and piroxicam [17]. They found 17 subjects (4.6%) exhibited delayed hypersensitivity to one of the NSAID preparations: 12 subjects (3.2%) had plaster test reactions to buprenorphine, 2 (0.5%) to etofenamate, 2 (0.5%) to indomethacin, and 1 subject (0.3%) to flufenamic acid. No subjects showed delayed hypersensitivity to ibuprofen. Allergic contact dermatitis has also been found to be relatively rare for transdermal NSAID therapies [23].

The effectiveness of the ibuprofen 200 mg plaster has been evaluated in a Phase 3 randomized clinical study for the treatment of adults ($N = 130$) with acute sports impact injuries/contusions [16]. The ibuprofen plaster was associated with a reduction in pain on movement compared with placebo ($p < 0.0001$). Algometry/tenderness measurements indicated that the ibuprofen plaster reduced tenderness/pain to a greater degree than placebo ($p < 0.0001$). Treatment-emergent AEs for the ibuprofen plaster were few ($\leq 1.5\%$) and were mild in severity.

The current study is limited by the small sample size and that it evaluated a smaller dose than that of the full-size of 14 cm $\times$ 10 cm 200-mg ibuprofen-medicated plaster. In

addition, majority of studies were Caucasian and it is not clear if the results are entirely translatable to other groups.

5. Conclusions

Under the conditions tested in this study, the safety parameters for both irritancy and contact sensitization of both ibuprofen and placebo plasters were considered acceptable. The ibuprofen-medicated plaster showed lower irritancy scores than the placebo plaster subjects, perhaps suggesting a beneficial irritancy protecting effect by ibuprofen on the formulation matrix and thus making the actual intended product less irritant than anticipated. This is supported by higher rates of discontinuation of placebo plaster subjects compared to those using ibuprofen-medicated plaster. The findings support the use of the ibuprofen plaster for the treatment of nonserious localized pain in adults.

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Declaration of interest

M Maganji is an employee of Reckitt Benckiser, MP Connolly was paid for his contribution to this research, A Bhatt is an employee of Reckitt Benckiser and a share holder. 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. Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

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