Drugs 2000 Feb; 59 (2): 245-249
0012-6667/00/0002-0245/$25.00/0

Lidocaine Patch 5%

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Contents

Abstract

▲ Lidocaine patch 5% comprises a soft, stretchy adhesive patch (10 by 14cm) containing 5% lidocaine (700mg) for the topical treatment of pain associated with postherpetic neuralgia (PHN).

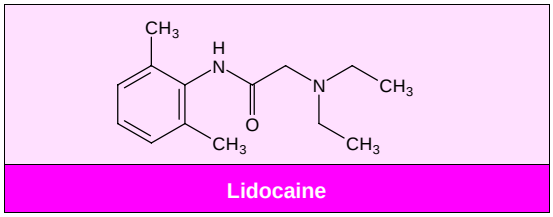
▲ Lidocaine provides analgesic relief by blocking neuronal sodium channels.

▲ Systemic absorption from lidocaine patch 5% is minimal in healthy subjects and patients with postherpetic neuralgia (3% of the dose is absorbed).

▲ In clinical trials (conducted over 12 hours to 24 days) involving patients with allodynia associated with PHN, treatment with lidocaine patch 5% resulted in a significant reduction in pain intensity and increased pain relief compared with vehicle patch.

▲ Lidocaine patch 5% was associated with few adverse events, the most frequent being mild skin redness or irritation at the application site which occurred with a similar incidence with lidocaine and vehicle patch.

Features and properties of lidocaine patch 5%	
Indication	
Postherpetic neuralgia	
Mechanism of action	
Local anaesthetic agent	Blocks voltage-gated sodium channels
Dosage and administration	
Dose per patch	5% (700mg)
Patch size	10 by 14cm
Recommended dosage	Up to 3 patches daily
Route of administration	Dermal
Site of application	Intact painful skin
Frequency of administration	Once daily for up to 12h
Pharmacokinetic profile (3 patches, 2100mg lidocaine, for 12h)	
Peak plasma concentration	0.13 mg/L
Time to peak plasma concentration	11h
Clearance	0.64 L/min
Plasma elimination half-life following intravenous administration	107 min
Adverse events	
Most frequent	Skin rash or redness at application site



Lidocaine

Postherpetic neuralgia (PHN) is a severely painful complication of herpes zoster. Approximately 20% of all patients with herpes zoster go on to develop long-lasting PHN (lasting several months to more than 3 years),[1] the prevalence increasing to 50 and 75% for patients over 60 and 70 years of age, respectively.[1,2] Patients with PHN characteristically describe a constant burning or aching sensation, intermittent lancinating pains, dysesthesia, and may report allodynia (pain provoked by innocuous stimuli) and sensory deficits.[1-3] The cause of PHN is not clearly understood, but postmortem studies suggest that patients with herpes zoster who are at risk of developing PHN have had dorsal horn atrophy, sensory ganglion fibrosis and cell, axon and myelin loss.[4]

Lidocaine (lignocaine) administered via a variety of routes (intravenous, intramuscular and transdermal) has been shown to provide relief from pain associated with PHN.[5-10] However, intravenous lidocaine 5 mg/kg can result in plasma concentrations that are associated with antiarrhythmic effects.[5,6] Topical application of lidocaine gel 5% to allodynic skin has been shown to relieve pain without serious systemic adverse effects.[7] A major drawback of this formulation, however, is the need for an occlusive dressing to cover the treated area; removal of this dressing has been associated with abrasions in over one-third of treated patients.[7] To avoid this problem a lidocaine patch (10 by 14cm) has been developed. This patch comprises a soft, stretchy, nonwoven polyester backing coupled with a layer of adhesive which contains lidocaine 5% (700mg per patch).[11] The patch was principally developed for use in patients with PHN, but is now also being tested for use in other forms of peripheral neuropathic pain.[12] Alternative uses of lidocaine patch 5% will not be discussed further in this profile.

1. Pharmacodynamic Profile

- Lidocaine is an aminoethylamide local anaesthetic which was first introduced in 1948. It blocks the voltage-gated sodium channels on excitable membranes, thereby preventing the generation and conduction of nerve impulses and providing analgesic relief.[13]

- Animal studies suggest that systemic lidocaine may exert its analgesic effect by selectively suppressing C-afferent fibre-evoked activity in the spinal cord,[14] or by suppressing spontaneous activity in damaged peripheral neurons.[15,16] As there is minimal systemic absorption of lidocaine from lidocaine patch 5%, it is not clear whether these mechanisms are relevant to the mechanism by which the patch exerts its analgesic effect.

- Pain relief of >50% was obtained in 9 of 12 patients with PHN who had lidocaine 1% or 2% administered by skin infiltration using a 27-gauge needle inserted into their area of maximum pain in a noncomparative study.[10] The 3 patients who did not respond had mild or no allodynia and continuous pain as their primary complaint.[10]

2. Pharmacokinetic Profile

- Systemic absorption of lidocaine from the patch is minimal. The amount absorbed is directly related to the skin surface area covered and duration of lidocaine patch application. At least 95% (665mg) of the lidocaine remains in a used patch, with absorption being $3 \pm 2\%$ of the dose applied to healthy volunteers.[11]

- The mean peak lidocaine plasma concentration achieved with lidocaine patch 5% (3 patches) was 0.13 mg/L after 11 hours in 15 healthy volunteers.[11] The minimum plasma concentration associated with antiarrhythmic effects is 0.6 mg/L,[17] and the minimum plasma concentration recommended for therapeutic antiarrhythmic efficacy is 1.5 mg/L.[18]

- Application of lidocaine patch 5% (3 patches) for 12 hours/day over 3 days did not increase sys-

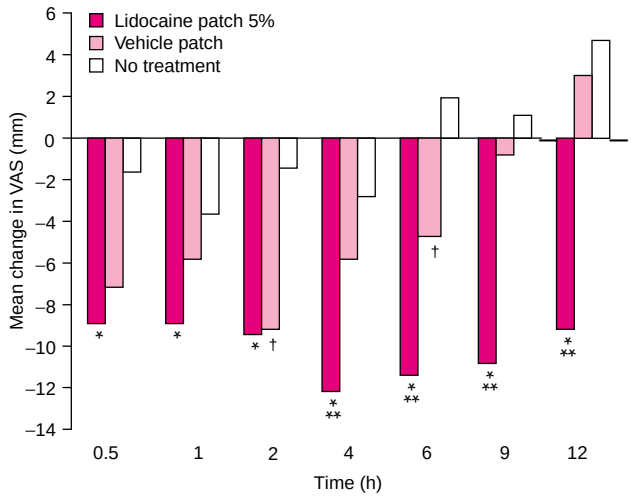


Fig. 1. Analgesic efficacy of lidocaine patch 5%, vehicle patch or no treatment in patients with postherpetic neuralgia. 35 evaluable patients used a single application of up to 3 patches containing either lidocaine 5% (700mg) or vehicle, or received no treatment (observation only) over a period of 12 hours in a randomised, double-blind, crossover trial. Changes in pain intensity were assessed using a 100mm visual analogue scale (VAS); a negative change indicates a reduction in pain intensity. Data estimated from a graph.[19] * p = 0.0001 to 0.021 *vs* no treatment; ** p < 0.001 to p = 0.038 *vs* vehicle; † p = 0.016 and 0.04 *vs* no treatment.

temic lidocaine concentrations compared with a single 12-hour application.[11]

- After intravenous administration of lidocaine (0.5 mg/kg) to healthy volunteers the average volume of distribution was 1.5 L/kg.[11]

- At low plasma concentrations (<1 mg/L) lidocaine is 70% bound to plasma proteins.[11]

- Lidocaine is primarily excreted via the kidneys after extensive hepatic metabolism (10% excreted unchanged). Mean systemic clearance was 0.64 L/min and mean plasma elimination half-life was 107 minutes after intravenous administration to healthy volunteers.[11]

3. Therapeutic Trials

Lidocaine patch 5% has been evaluated in 3 randomised, double-blind trials in patients with PHN. In these trials PHN was defined as pain persisting for at least 1 month after healing of herpes zoster-associated rash. All patients enrolled in the clinical studies had had PHN for 4 months to 29 years, and had a well-defined area of allodynic skin on the torso or limbs.[19-21] Studies ranged in duration from 12 hours to 4 weeks. Pain intensity was assessed using a 100mm visual analogue scale (VAS); higher scores represent more intense pain. In all studies a 6-point categorical scale was also used to rate pain relief: 0 = worse pain; 1 = no pain relief; 2 = slight pain relief; 3 = moderate pain relief; 4 = a lot of pain relief; and 5 = complete relief. Patients were not permitted to use any other topical medicated salves or creams, but were allowed to continue treatment with oral analgesics.

- During a single 12-hour application, lidocaine patch 5% (up to 3 patches) significantly reduced mean VAS scores compared with vehicle patch from 4 to 12 hours ($p < 0.001$ to $p = 0.038$) and no treatment at all evaluation time-points ($p < 0.0001$ to $p = 0.021$) in a crossover study involving 35 evaluable patients (fig. 1).[19]

- Pain relief scores were also significantly higher with lidocaine patch 5% than with vehicle patches ($p = 0.033$) or with no treatment ($p < 0.0001$). However, vehicle patches also produced significantly greater pain relief on average than no treatment

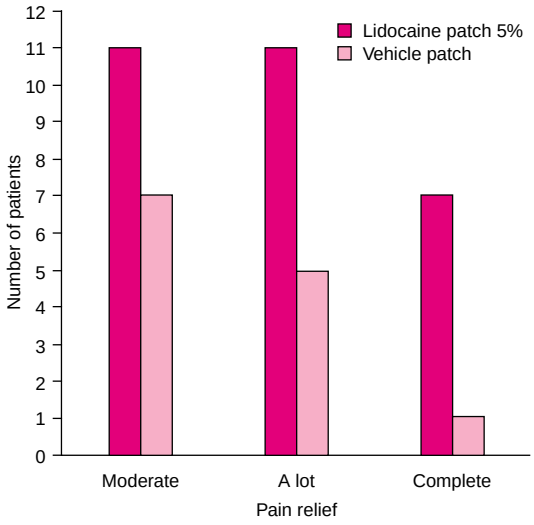


Fig. 2. Number of patients with postherpetic neuralgia reporting moderate or greater pain relief following treatment with lidocaine patch 5% (700mg) or vehicle patch. 32 evaluable patients received treatment with up to 3 patches containing either lidocaine 5% or vehicle applied for 12 hours per day for up to 14 days in a randomised, double-blind, crossover trial. All patients had previously received successful treatment with lidocaine patch 5%. Patients rated pain using a 6-point categorical scale: 0 = worse pain; 1 = no pain relief; 2 = slight pain relief; 3 = moderate pain relief; 4 = a lot of pain relief; and 5 = complete relief.[20]

(p = 0.001), a finding which was attributed to the adhesive patches reducing painful external mechanical stimulation of patients' allodynia.[19]

• The efficacy of lidocaine patch 5% was demonstrated in a randomised, double-blind crossover study of 32 evaluable patients who had used patches regularly for at least 1 month prior to the trial on a compassionate-use basis and reported at least moderate pain relief.[20] In this study, patients applied the same number of patches as prior to the study (usually 3 per day) for 12 hours each day. Each treatment phase lasted up to 14 days, with no washout period between treatments. The primary efficacy variable was time to exit; this was defined as the length of time taken until a patient reported a decrease of 2 or more categorical pain relief scores for 2 consecutive days, at which point the patient exited from that treatment phase. Time to exit was significantly longer with lidocaine patch than vehicle (median >14 *vs* 3.8 days; $p < 0.001$). Pain relief was reported as moderate or greater by 29 patients using the lidocaine patch versus 13 patients using vehicle (fig. 2). 78.1% of the patients preferred lidocaine patch for pain relief, 9.4% preferred the vehicle patch ($p < 0.001$) and 12.5% had no preference.[20]

• In a 2-centre, double-blind, randomised study, 150 patients with PHN and allodynia were treated with either lidocaine patch 5% or vehicle patch for 4 weeks. Lidocaine patch caused a VAS reduction of 12mm at 4 hours and 20mm after 8 days; this reduction was sustained for the duration of the study period (4 weeks). VAS scores, pain relief ratings and allodynia scores showed that lidocaine patch 5% was significantly superior to vehicle patch ($p < 0.005$), although vehicle patch also produced reductions in VAS scores from prestudy levels (data not specified).[21]

4. Tolerability

• Lidocaine patch 5% is well tolerated according to data from clinical trials.[19,20]

• The most frequently reported adverse event was mild to moderate skin redness, rash or irritation at the patch application site; this was associated with both lidocaine and vehicle patches. In 1 double-blind, crossover trial that included 32 evaluable patients, skin redness or rash was reported by 9 and 11 lidocaine and vehicle recipients, respectively, over the 14-day treatment periods.[20] In another double-blind crossover trial that included 35 patients, skin reddening at the application site was reported by 2 patients (1 with lidocaine, 1 with vehicle). Patch removal was well tolerated, with patients reporting only minor, transient increases in pain.[19]

• Systemic absorption of lidocaine from the patch through intact skin is minimal (section 2). None of the known systemic effects of lidocaine (altered CNS or cardiovascular function) have been reported in patients using lidocaine patch 5%.[11]

5. Lidocaine Patch 5%: Current Status

Lidocaine patch 5% has shown efficacy for the topical treatment of peripheral pain associated with PHN, and is generally well tolerated. Ongoing clinical trials are evaluating its efficacy in a number of other chronic peripheral pain syndromes.

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