

# Lidocaine

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## Introduction

Painful peripheral neuropathy is a common complication of diabetes that is often difficult to treat. Typically, treatment involves varying combinations of opiates, tricyclic antidepressants and anticonvulsants. Factors including side effects, drug interactions and patient adherence often limit control of symptoms.

Topical lidocaine therapy has been used for the treatment of postherpetic neuralgia for some time. No large scale trials have been carried out reviewing the use of topical lidocaine therapy in diabetic peripheral neuropathy, but there is evidence to suggest that topical lidocaine therapy may be a treatment option for painful diabetic peripheral neuropathy.

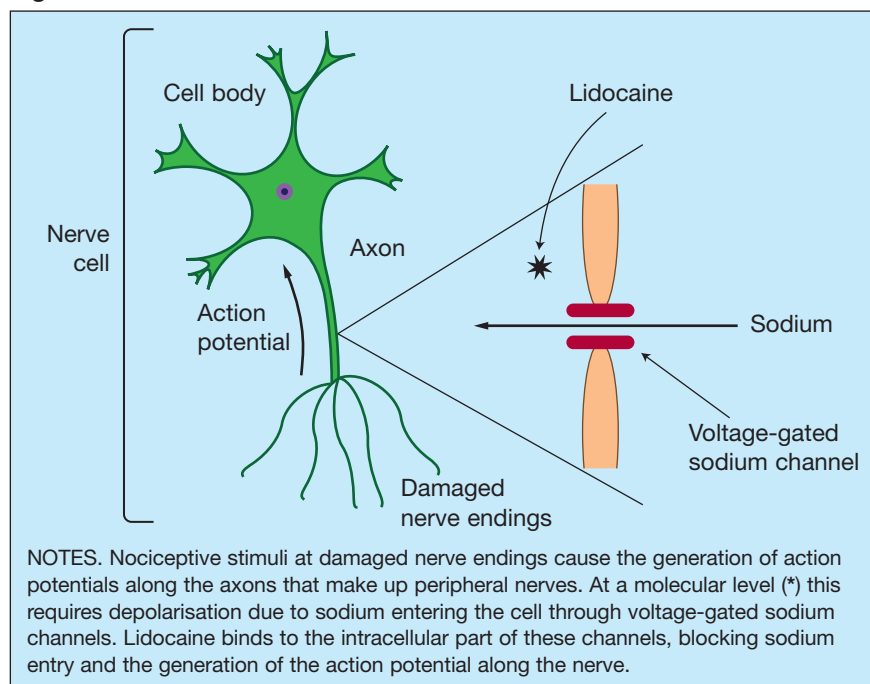
## Pharmacology

Figure 1 outlines the pharmacological action of the topical anaesthetic lidocaine. It acts directly on nerve cells to block conduction of impulses down axons, therefore blocking transmission of nociceptive signals. Structurally, lidocaine contains a hydrophilic amide and a hydrophobic aromatic portion allowing it to diffuse to the nerves and through perineural tissue.

At a molecular level, lidocaine binds to voltage-gated sodium channels. This binding occurs at the intracellular surface. By binding to the channel, sodium influx is blocked and the depolarisation required for action potentials to be generated is inhibited. As a result, impulse conduction is blocked.

Local anaesthetics such as lidocaine are weak bases, requiring a local pH of between 8 and 10 for efficacy. Clinically, a common comorbidity in diabetic peripheral

Figure 1. Mechanism of action of lidocaine



neuropathy is ulceration/local tissue infection. This results in a localised metabolic acidosis, dropping the pH and reducing the ability of the lidocaine to permeate through cell membranes, thus reducing its clinical effect.

Topical use of the drug has relatively few systemic side effects. The drug is either resorbed through the capillaries into the vasculature and hepatically cleared, or metabolised locally. Following this, nerve function returns to its previous state.

## Trials of safety and efficacy

A number of randomised controlled trials have now demonstrated the tolerability and effectiveness of 5% lidocaine patches for the treatment of postherpetic neuralgia (PHN).

In a double-blind, randomised, placebo cross-over trial comparing

lidocaine patch to a placebo vehicle patch in the treatment of PHN, 32 patients suffering from PHN were randomised into two groups, one receiving lidocaine patch and the other placebo.<sup>1</sup> The trial consisted of two phases (placebo phase/lidocaine phase), each for a maximum of 14 days. Patients in both groups underwent daily assessment of their pain control via interview using a six-point Pain Relief Scale (5 = complete relief of pain, 4 = a lot of relief, 3 = moderate relief, 2 = slight relief, 1 = no change, 0 = worse pain). During the trial, a total of three patches were applied to the area of pain. A pain score deterioration of two or more points over two or more days led to exit from a trial phase. The mean outcome measure was average time to exit each phase. For the lidocaine patch this was 14 days,

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and 3.8 days for the vehicle patch. Twenty-nine of the trial patients (90%) reported a pain score of four to five for at least five days.

In a similar randomised, double-blind, placebo-controlled study, 58 patients were recruited and treated in two trial phases with lidocaine or placebo.<sup>2</sup> Participants had a variety of underlying pathologies causing neuropathy, including PHN, meralgia paraesthetica and post-surgical neuralgia. Evaluation of the patch efficacy involved an assessment of pain score and quality of sleep. The results of this study confirmed a reduction in pain and improvement in sleep quality during the lidocaine treatment phase. Data produced suggested that the number needed to treat (NNT) for one patient to have a 50% reduction in pain was 4.4, and for a pain reduction of 30% the NNT was 3.6.

### Specific evidence for use in diabetes

There are few trials exclusively reviewing the efficacy of 5% lidocaine patches in the treatment of painful diabetic peripheral neuropathy. There are no randomised controlled trials that we could find in the literature.

In an open-label study, with flexible dosing using 5% lidocaine patch therapy in painful diabetic peripheral neuropathy, 53 patients were studied for a three-week duration.<sup>3</sup> Inclusion criteria included a greater than three-month duration of neuropathy pain, Brief Pain Inventory (BPI) rating of >4, and stable analgesic regimen for at least one week. Patients with open wounds or previous lidocaine treatment were excluded. The primary outcome variable was the change in mean daily pain diary ratings from baseline to week three. Secondary outcome measures of change from baseline to week three and baseline to week eight included the additional pain measures (Short Form McGill Pain Questionnaire [SF-MPQ], pain quality and intensity scales and BPI pain relief), the health-related quality-of-life (QOL) measures (sleep quality, pain interference, depression and mood), and assessments of safety and tolerability.

### Key points

- Topical lidocaine acts in peripheral neuropathic pain to block nerve conduction and suppresses spontaneous ectopic discharge from damaged peripheral nerves
- Topical therapy can produce significant reductions in patient perceived pain scores, without the need for dose titration or the development of systemic side effects
- There is a need for a randomised controlled trial to confirm effectiveness of use in painful diabetic peripheral neuropathy

Patients applied four patches daily, for 18 hours. Patients recorded daily pain scores. During the three-week study period, patients were not allowed to titrate their other analgesics, which included opiates and tricyclics.

The results showed that 70% (37) of patients had a reduction in pain of at least 30% from baseline to week three. No dose titration of patches was needed to achieve these results. The pain reduction was also accompanied by improvement in sleep quality and BPI score. Twenty-eight of the patients underwent an additional five-week study period during which they were allowed to alter the dosages of their usual pain medications as required. None of these patients had to increase their analgesics and several reduced their dosages. Three patients were able to discontinue other treatments, including amitriptyline and gabapentin.

From the trials described here, including those in PHN, no severe adverse effects of 5% lidocaine patches were noted. In all of the trials there were reports of local skin reactions with the patch. Reactions included burning, itch and local rash. The incidence of these was variable but, in one placebo-controlled trial, the vehicle placebo patch had a similar incidence of local reactions.<sup>1</sup> No systemic side effects were noted in any of the trials. In the open-label diabetes study,<sup>3</sup> peak lignocaine concentrations 12 hours post application of patch were well below 1.5µg/ml (the level associated with a potential antiarrhythmic effect). A further safety study<sup>4</sup> confirmed safe blood levels of lidocaine with a dose of four patches/

18 hours per day (the dose licensed for PHN by the US Food and Drug Administration).

### Discussion

There is established evidence that topical lidocaine therapy is effective in the treatment of peripheral neuropathic pain syndromes, particularly PHN. This therapy has been shown to improve pain control and quality of life. It is a well tolerated therapy with no systemic side effects reported. All side effects reported were localised to site of application.

Some evidence is available that shows positive outcomes on pain control in patients with painful diabetic peripheral neuropathy, but a large scale, randomised clinical trial is required to confirm the benefits.

### Conflict of interest statement

There are no conflicts of interest.

### References

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