Commentary

How does topical lidocaine relieve pain

1. Introduction

The report by Krumova et al. in this issue [6] raises important questions about the neural signaling involved in neuropathic pain, and highlights the presence of substantial gaps in our knowledge about how topical lidocaine relieves pain. The authors studied the sensory effects of applying an adhesive patch containing 5% lidocaine (Versatis® 5%) to the skin in normal subjects. The study was double blind and used a validated sensory testing protocol to assess affects on thermal and mechanical sensibility. The authors quantitatively corroborate the clinical impression that though topical lidocaine may relieve neuropathic pain [8], the effects on sensation are minimal. The study was performed after only six hours of application of the study medication, and one might quibble that this testing interval is insufficient to achieve full effects. Nevertheless it is quite striking that the patch produced no measurable effect on tactile (large fiber) function, and the effects on pain sensibility were typically mild. These findings raise broad questions about the primary afferent mechanisms that contribute to neuropathic pain. In particular, since, the effects of topical lidocaine on clinical pain are often disappointing, are the limitations of therapy driven by its modest sensory effect (and in a sense under-dosing), or is there some other basis for the limited efficacy of topical lidocaine?

2. What do the effects of lidocaine teach us about the cause of neuropathic pain?

It is useful to reflect on the paradox inherent in neuropathic pain. Most neuropathic pain conditions are associated with impairment of nociceptive function. Why is loss of nociceptive function associated with a gain in function (viz., pain)? As lidocaine applied topically to the skin may, with sufficient dosing, be expected to further decrease sensibility, should more numbness relieve pain? Should further loss of function lead to pain relief?

Henry Head, the prominent English neurologist of the early 1900s, considered pathological pain to be a release phenomenon [5]. He suggested that a loss of large fiber function led to loss of inhibition in the CNS and an amplification of the inputs from nociceptors. There may be something to this. Thus, when action potential conduction in cold fibers is blocked by pressure on a peripheral nerve, a cooling stimulus may, in fact, evoke a burning sensation [9].

In general, what one observes, however, is that painful neuropathies involve effects on nociceptive fibers, without necessarily affecting large diameter fibers (tactile functions). Neuropathies restricted to small fibers, as may be seen, for example, in some patients with diabetes, are often associated with pain. Large fiber neuropathies typically are not. The gate control theory, which emphasizes loss of large fiber input as the basis for pain, does not help us explain neuropathic pain where large fiber function may be unaffected [7].

Clearly, inflammatory pain stems from nociceptor sensitization. The case can be made that neuropathic pain does as well. The loss of nociceptor function seen, for example, in a painful traumatic neuropathy may in a sense be irrelevant. There is no paradox if we consider that neuropathic pain probably reflects not the dead nociceptors, but rather the overriding effects of the sensitized nociceptors. Pathological pain equals abnormal discharge somewhere along nociceptive pathways initiated directly by the underlying disease. Thus a therapy that decreases nociceptor function is expected to work even though in a sense it amplifies the nociceptor dysfunction.

3. How can lidocaine relieve allodynia?

Evidence indicates that touch-evoked pain is A-beta mediated [3]. If we accept that topical lidocaine has no effect on tactile sensibility, and that allodynia is a prominent part of neuropathic pain, how can lidocaine help patients with post-herpetic neuralgia where allodynia is an important part of the clinical presentation? The answer to this is that allodynia is likely driven by central sensitization. If the nociceptor discharge is removed, then large fiber activation lacks synaptic efficacy centrally, and allodynia disappears. Therefore, if topical lidocaine knocks down nociceptor discharge at the level of the skin, then light mechanical stimulation evokes feelings of touch, but not pain. If this is the case then Henry Head got it wrong 100 years ago. That is, pain is not a release phenomenon evolving from loss of large fiber function, as was also suggested in the gate control theory. To the contrary, large fiber activation actually induces pain because of CNS plasticity. Remove the nociceptor input and this central sensitization is attenuated.

4. Does efficacy of topical lidocaine depend on some level of anesthesia?

Obviously, lidocaine may block sodium channels to the point that there is dense anesthesia. However, blunting of normal pain sensibility in the skin from lidocaine may be considered more of an unwanted side effect. Multiple lines of evidence, in fact, suggest that an abnormal expression of sodium channels contributes to neuropathic pain. Conceivably the pathological activity of these sodium channels is susceptible to doses of lidocaine that are insufficient to block normal function of the nociceptors [4]. In other words, lidocaine effects on neuropathic pain probably do not require anesthesia. Consistent with this hypothesis, intravenous
lidocaine and oral therapy with the lidocaine analogue, mexiletine, relieves pain in some patients. Neither of these therapies significantly affects normal sensation.

5. Where does the abnormal signaling arise?

Where along the neural axis do the signals for neuropathic pain arise? It is not immediately obvious why treating the skin should have an effect on neuropathic pain. After all, in nerve injury models the injury is “upstream” from the skin. We now understand this paradox in some detail [1,2,10]. The “intact” or uninjured nociceptors that reach the skin after nerve injury serve partly denervated tissue. Denervation leads to upregulation of molecules such as nerve growth factor (NGF). The hypothesis is that NGF and other upregulated cytokines and growth factors sensitize the surviving nociceptors, inducing spontaneous activity. This spontaneous activity induces central sensitization accounting for other phenomena, including allodynia. The contribution of Schwann cells, which contain multiple C-fibers should also be considered. For example, injury to nerve may in a sense partly denervate Schwann cells (Wallerian degeneration of some but not all of the C-fibers in a given Schwann cell). Therefore, if these partly denervated Schwann cells act to sensitize the neighboring “intact” C-fibers, then sensitization could also occur along the course of the nerve.

6. Are there limits of topical lidocaine therapy?

The Krumova study clearly indicates that the 5% lidocaine patch induces limited sensory changes. Could more anesthesia lead to more pain relief? One way to study this would be to do a distal sensory nerve block. For example, in a patient with neuropathic foot pain, if one were to perform a nerve block distal to the saphenous, peroneal, sural, and posterior tibial nerves, so as to provide dense anesthesia, but observe that the pain still persists, then the signaling for pain must originate proximally, along the neural axis. Does failure of topical lidocaine to relieve pain in a given patient reflect inadequate delivery of the drug to the skin, or does failure mean that the skin is not where the pain signals are arising? Amazingly, and disappointingly, we really do not know the answer.

Conflict of interest statement

The author has direct financial interests in the development of topical therapies for the treatment of pain (Arcion Therapeutics).

References


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