Original Article

Mexiletine Therapy for Chronic Pain: Survival Analysis Identifies Factors Predicting Clinical Success

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Abstract
Mexiletine, a sodium channel blocker, treats neuropathic pain but its clinical value has been questioned due to its significant side effects and limited efficacy. We hypothesized that ongoing therapy with mexiletine would have limited patient acceptance, but that an analgesic response to intravenous (IV) lidocaine (a pharmacologically similar drug) would identify patients most likely to choose ongoing therapy with mexiletine. We identified a cohort of 37 patients with neuropathic pain who underwent IV lidocaine infusions at our institution and were subsequently prescribed mexiletine. Time until discontinuation of mexiletine was used as the primary endpoint. Time until discontinuation is a clinically relevant, discrete, objective endpoint gaining acceptance as a metric for assessing clinical performance of drugs with significant side effects and limited efficacy. We used the techniques of survival analysis to determine factors that predicted continued therapy with mexiletine. Median time to discontinuation of mexiletine was only 43 days. A stronger analgesic response to IV lidocaine significantly predicted continued acceptance of mexiletine therapy. Decreasing age and male gender also predicted continued acceptance of mexiletine therapy. Analyzing time to mexiletine discontinuation uncovers important limitations in mexiletine's clinical performance missed by studies with conventional endpoints, such as change in pain score. Despite claims of efficacy, acceptance of mexiletine therapy is poor overall. Test infusions with lidocaine identify patients most likely to continue mexiletine therapy. Further work is needed to confirm these results and evaluate the relative acceptance of mexiletine vs. other treatments of neuropathic pain. J Pain Symptom Manage 2008;35:321–326.

Key Words
Pain, neuropathic pain, mexiletine, intravenous lidocaine, lidocaine, survival analysis, chronic pain

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Introduction

Mexiletine is a class IB sodium channel blocker used to treat chronic neuropathic pain, a disorder afflicting 5.5 million Americans.[1] Tremont-Lukats et al. recently confirmed mexiletine's analgesic efficacy for neuropathic pain in a meta-analysis.[2] However, mexiletine induces nausea in up to 40% of patients and dizziness in up to 26% of patients.

Previous studies of oral mexiletine treatment have focused on conventional analgesic endpoints without integrating factors promoting treatment failure, such as side effects. These studies have focused on narrowly defined measures of efficacy (e.g., relief of spontaneous pain or mechanical allodynia) but have not captured an overall measure of mexiletine's clinical performance. In the absence of a more global measure indicating that mexiletine's limited efficacy offsets its prominent side effects, experts have recently questioned its clinical value.[3] One clear clinically relevant indication of overall treatment failure with mexiletine is the choice to discontinue it. Therefore, time until mexiletine discontinuation can be used as a discrete measure of overall mexiletine performance, integrating factors both promoting and discouraging continued treatment.

No studies have measured the proportion of patients who accept chronic therapy with mexiletine or what factors predict acceptance vs. discontinuation. Previous pilot studies of mexiletine used response to intravenous (IV) lidocaine, another class IB sodium channel blocker, to predict subsequent mexiletine response, as defined by relief of spontaneous pain[4] or mechanical allodynia.[5]

On the basis of mexiletine's limited efficacy and prominent side effects, we hypothesized that most patients with neuropathic pain would not accept chronic therapy with mexiletine. We further hypothesized that patient discontinuation of chronic mexiletine therapy could be predicted by poor results from a previous analgesic IV lidocaine test infusion.

To test our hypotheses, we conducted a retrospective cohort study of neuropathic pain patients who were treated with mexiletine following a lidocaine infusion at the Stanford Pain Management Center. Patient acceptance of mexiletine therapy was evaluated by measuring time to discontinuation. Time to discontinuation is a direct indicator of patient acceptance of chronic therapy and has been espoused as a clinically relevant, discrete composite endpoint of efficacy and side effects.[1,6–8] We analyzed time to discontinuation of mexiletine therapy using the tools of survival analysis (Kaplan-Meier and Cox proportional hazards) to determine factors responsible for failure of chronic mexiletine therapy.

Methods

Design and Setting

We conducted a retrospective cohort study of patients who had undergone IV lidocaine infusions for treatment of neuropathic pain at the Stanford Pain Management Center, a tertiary referral-based pain management center. The study was approved by our institutional review board.

Study Participants

Patients were identified retrospectively by screening sequential charts of patients currently under treatment at the Stanford Pain Management Clinic. We randomly selected three separate starting points in the alphabet—charts that began with the letters A, K, and R. Three starting points were used to reduce the possibility of bias being introduced by selecting only names that began with a particular letter (which might enrich for specific ethnic groups). All patients who were prescribed mexiletine were included in the analysis. Patients were referred for IV lidocaine infusions based on findings suggestive of neuropathic pain, including hyperalgesia, allodynia, hypoesthesia, and hyperesthesia.

Lidocaine Infusions

Patients had an IV catheter placed. Then, during approximately one hour, they received a stepwise, computer-controlled lidocaine infusion to a targeted plasma level of 5 mcg/mL using a paradigm previously developed in our institution.[9] At the time of the infusion, a record was completed for all patients documenting initial and final Numerical Rating Scores (NRS) of pain. Blood pressure and