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Therapeutic drug monitoring of mexiletine at a large academic medical center

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Abstract

Introduction: The therapeutic trough range for mexiletine (0.8–2 mcg/mL) was largely established in the setting of arrhythmia prophylaxis following myocardial infarction.

Objective: Describe the usage patterns of serum mexiletine concentrations and the impact of these concentrations on mexiletine dosing in modern practice for ventricular arrhythmia treatment.

Methods: A single-center, retrospective analysis was conducted using the electronic medical record to identify serum mexiletine concentrations drawn between December 2004 and December 2014. The primary endpoint was the incidence of mexiletine concentrations drawn as troughs. Secondary outcomes included the incidence of mexiletine concentrations that prompted a dose change, association between adverse events and elevated concentrations, and association between baseline characteristics and mexiletine concentrations.

Results: A total of 237 individual concentrations were included for analysis with 109 (46.0%) drawn appropriately as trough concentrations. Only 31 (13.1%) of the 237 concentrations drawn prompted a dose change. Mexiletine was primarily used for the treatment of ventricular arrhythmias (96.2%), and 108 (45.6%) concentrations were drawn in an effort to assess efficacy. The median concentration was statistically different between patients with and without an adverse event (0.8 vs 0.7 mcg/mL, respectively; $p = 0.017$), but may not represent a clinical significance. Patients with hepatic dysfunction had higher median concentrations compared to those without hepatic dysfunction (1.30 vs 1.07 mcg/mL; $p = 0.01$).

Conclusion: Mexiletine concentrations are often drawn at inappropriate times and seldom influence a dose change. This study suggests that routine monitoring of mexiletine concentrations may not be necessary; however, therapeutic drug monitoring may be considered in patients with hepatic dysfunction or to confirm mexiletine absorption in patients where this represents a concern.

Keywords

Cardiovascular, therapeutic monitoring, antiarrhythmics, drug monitoring

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Introduction

Mexiletine is an oral Vaughan-Williams class IB antiarrhythmic used in contemporary practice for the suppression of ventricular arrhythmias from various etiologies. Studies completed in the 1970s and 1980s suggested a correlation between serum mexiletine concentrations and toxicity, but varied in peak, random, or trough concentrations.[1–6] A mexiletine trough range of 0.8–2 mcg/mL is used currently as the goal therapeutic range based on this literature; however, most of these studies were mainly performed in the post-myocardial infarction population for prophylaxis of ventricular tachycardia (VT) which is inconsistent with modern use of this medication.[2,7] Therapeutic drug monitoring in contemporary practice is complicated by the wide range in which toxicity has been reported (0.41–4.4 mcg/mL). The complex nature of mexiletine monitoring would favor therapeutic drug monitoring, but there is a

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paucity of data in contemporary use. The purpose of this study is to describe mexiletine concentrations in current practice, the rationales of therapeutic drug monitoring, and the impact of these concentrations on patient care.

Methods

A single-center, retrospective analysis was conducted using the electronic medical record to identify mexiletine concentrations from December 2004 to December 2014. Concentrations were included if they were drawn in patients who were older than 18 years of age and had consented to the use of their medical information for research. Multiple concentrations per patient were analyzed if they were from different hospitalizations or during the same hospitalization if organ function had acutely changed. Subsequent levels for the same patient during the same hospitalization purely drawn for surveillance were excluded. Mexiletine levels lacking complete information or involving laboratory error were excluded. In accordance with the amended Declaration of Helsinki, this study was approved by the Mayo Clinic Institutional Review Board (PR14-00925).

Mexiletine trough concentrations were defined as any level drawn within 2 h prior to the next dose or expected next dose. A concentration drawn within 2 h after a given dose was considered a peak concentration. Anything outside of those parameters was considered a random concentration. Elevated liver function tests were defined as greater than three times the upper limit of normal. History of hepatic dysfunction was defined as a chronic diagnosis of liver failure or cirrhosis.

Serum mexiletine concentrations were performed by Mayo Medical Laboratories. Mexiletine is extracted with an organic solvent from the serum at neutral or basic pH. The organic extract is acidified and evaporated to be taken up and chromatographed by reverse-phase high-performance liquid chromatography. Detection is then determined by absorbance at 210 nm and quantified by peak–height ratios relative to an internal standard (p-chlorodisopyramide).[8]

Baseline characteristics are presented in median and interquartile ranges (IQRs). Nominal data were evaluated with chi-square or Fisher's exact test. Medians were compared using Mann–Whitney test.

Results

A total of 488 mexiletine concentrations were identified during the study period, of which 237 concentrations were included in the analysis representing 121 unique patients (Figure 1). The baseline characteristics (Table 1) show the study population was mostly males (79.1%) with reduced ejection fraction (84%). The predominant indication for the use of mexiletine in this population was for suppression of VT (96.2%) with three times a day dosing frequency being the most common (87.4%). Overlap of intravenous (IV) lidocaine with mexiletine represented a transition from IV to oral therapy in the majority of patients. Patient on concomitant amiodarone therapy had a median level of 0.7 (IQR = 0.5–1.1) mcg/mL. The primary reason for therapeutic drug monitoring of mexiletine was to assess efficacy as stated in patient charts (45.6%) followed by monitoring with a concern for an adverse event (21.9%; Table 2). A possible adverse event was present in 45.4% of the total levels drawn.

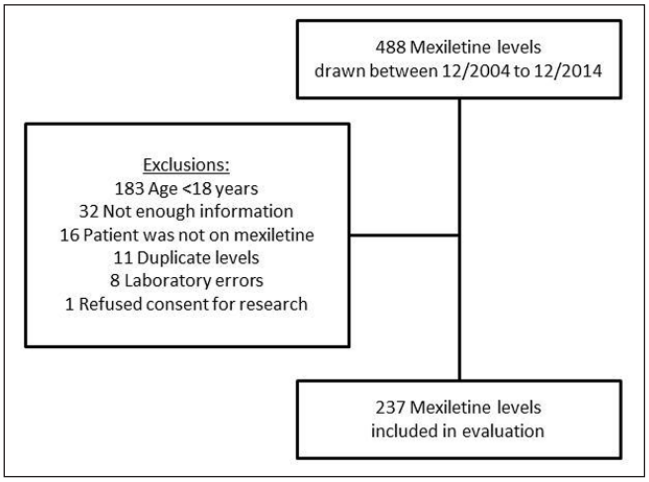

Figure 1. Consort diagram.

Most mexiletine concentrations were determined to be outside of the recommended range of 0.8–2 mcg/mL, with 51.7% being subtherapeutic. Only 46% of the levels were considered trough concentrations. The therapeutic drug monitoring of mexiletine influenced a dose change in 13.1% of all concentrations drawn. Twenty of the 31 dose changes (64.5%) were dose increases due to low serum concentrations and need for additional arrhythmia control. Additionally, nine patients had dose reductions (four patients) or discontinuations (five patients). The remaining two changes in dose involved restarting mexiletine after realizing the level was not supratherapeutic.

Patients with elevated liver function tests to greater than three times the upper limit of normal and a history of hepatic dysfunction were associated with statistically significantly higher mexiletine concentrations ($p = 0.002$ and 0.046, respectively). The median concentration for patients with elevated liver function test was 1 mcg/mL compared to 0.7 mcg/mL for those with normal liver function. The median concentration for patients with a history of hepatic dysfunction was 1.3 mcg/mL compared to 0.7 mcg/mL for those without a history of hepatic dysfunction. Mexiletine 150 mg three times a day represented the most common dosing strategy in patients with hepatic dysfunction, elevated liver function tests, and normal liver function tests. Comparing patients who had an adverse event to those who did not, there was a statistically significant difference in median mexiletine levels (0.8 mcg/mL (IQR = 0.6–1.2) vs 0.7 mcg/mL (IQR = 0.5–1); $p = 0.017$).

Table 1. Baseline characteristics of patients for each mexiletine concentration (N = 237).

Baseline characteristics	n (%)[a]
Age (years)	64.6 (55.6, 72.9)
Male (sex)	189 (79.1)
Weight (kg)	89 (74.6, 104)
Body mass index (kg/m^2)	28.9 (25.3, 32.9)
Ejection fraction <40%	200 (84.0)
Heart failure with preserved ejection fraction	9 (3.8)
Coronary artery disease	122 (51.3)
Diabetes mellitus type 2	77 (32.4)
Hypertension	137 (57.6)
Concomitant antiarrhythmics	171 (71.9)
Lidocaine	23 (9.7)
Amiodarone (oral at time of level)	127 (53.4)
Amiodarone (IV at time of level)	16 (6.7)
Procainamide	6 (2.5)
Quinidine	8 (3.4)
Sotalol	19 (8.0)
Dofetilide	2 (0.8)
Disopyramide	0
Dronedarone	0
Serum creatinine (mg/dL)	1.3 (1.1, 1.85)
Elevated liver function tests (3× ULN)	24 (10.2)
Elevated bilirubin (3× ULN)	36 (15.3)
History of hepatic dysfunction (3× ULN)	18 (7.7)
Indication	
Ventricular tachycardia	229 (96.2)
Prophylaxis	1 (0.4)
Other	8 (3.4)
Chronic use of mexiletine at time level was checked	165 (69.6)
Frequency of dosing	
Daily	2 (0.8)
BID	18 (7.5)
TID	208 (87.4)
QID	8 (3.4)
Other	2 (0.8)
Total daily dose (mg)	
Median dose	450 (450, 600)
Max dose	1050
Min dose	150

BID: twice daily; IQR: interquartile range; TID: thrice daily; ULN: upper limit of normal; QID: four times daily.
[a]Results are displayed as median (IQR) or number (%) unless otherwise noted.

Table 2. Results (N = 237).

Variable	n (%)
Reason for mexiletine concentration	
Efficacy	108 (45.6)
Concern for adverse event	52 (21.9)
Chronic therapy monitoring	39 (16.5)
Unable to determine	38 (16.0)
Concentration (mcg/mL)	
<0.8	123 (51.7)
0.8–2	106 (44.5)
>2	9 (3.8)
Type of concentration	
Trough (<2 h before dose)	109 (46.0)
Random	85 (35.9)
Peak (<2 h after dose)	19 (8.0)
Unable to determine last mexiletine dose	24 (10.1)
Concentration drawn at steady state	220 (94.8)
Dose change occurred because of concentration	
No	189 (79.7)
Yes	31 (13.1)
Unable to determine	17 (7.2)
Adverse events	
None	130 (54.6)
Dizziness/lightheadedness	23 (9.7)
Ataxia	4 (1.7)
Paresthesia	2 (0.8)
Blurred vision/visual disturbances	4 (1.7)
Tremors	9 (3.8)
Insomnia	1 (0.4)
Somnolence/altered mental status	9 (3.8)
Nausea	28 (11.8)
Emesis	8 (3.4)
Constipation	2 (0.8)
Diarrhea	8 (3.4)
Other	29 (12.2)

Discussion

In this single-center, retrospective study, serum mexiletine concentrations were often drawn inappropriately, with only 46% of concentrations drawn as troughs, which complicates their interpretation. The majority of serum concentrations (51.7%) were below the recommended therapeutic range; however, only a minority, 13.1%, of all levels influenced a dose change. The majority of medication therapy adjustments were made prior to finding out the actual results of the mexiletine serum concentration, and thus decisions were largely based on clinical assessment alone. Since this was a retrospective study, it was not possible to determine whether decisions were reevaluated when the concentration was available.

The adverse event rate of 45.4% seen in our study is in accordance with the manufacturer-reported adverse events in the package insert.[9] Interestingly, the majority of patients experiencing an adverse event had a median mexiletine concentration within the therapeutic concentration range and only 3.8% of all levels were greater than the upper limit of the therapeutic range. Although patients who experienced an

adverse event related to mexiletine had a statistically significant higher serum mexiletine concentration than did patients without an adverse event, the absolute difference was merely 0.1 mcg/mL (0.8 vs 0.7 mcg/mL, respectively; p = 0.017), and the clinical significance of this difference is difficult to assess. These results are, however, consistent with several studies demonstrating that higher mexiletine concentrations are associated with a higher incidence of adverse events.[1,3]

Patients with hepatic dysfunction and elevated liver function tests experienced higher serum mexiletine concentrations compared to patients without these comorbidities. This observation corroborates the findings by Nitsch et al.[5] which demonstrated that the presence of liver cirrhosis portended higher mexiletine concentrations compared to the control group. This reflects the importance of hepatic metabolism of mexiletine and less reliance on kidney elimination.[10,11] With adverse effects occurring within the therapeutic range, the clinical implications of monitoring mexiletine concentrations in this patient population is unknown without further studies.

The concomitant use of amiodarone with mexiletine could theoretically raise mexiletine concentrations through inhibition of CYP1A2. In this study, the theoretical increase was not observed, where the median mexiletine concentration in patients receiving concomitant amiodarone therapy was 0.7 (IQR = 0.5–1.1) mcg/mL.

This retrospective study suggests that mexiletine is most often utilized as adjunct therapy for the treatment of VT in contemporary practice. The serum concentrations achieved are lower than the previously established range of 0.8–2 mcg/mL. As shown in this study, the presence or absence of suspected or known mexiletine related adverse events may play a larger role in dosing strategies rather than the actual mexiletine concentrations. However, thoughtful monitoring of mexiletine trough concentrations may be considered in certain patients. Hepatic dysfunction was found to be associated with an increased risk of elevated mexiletine concentration, but the clinical implications of this finding would require further studies. If a mexiletine concentration is checked, a trough concentration is preferred, defined as a level drawn within 2 h of the next scheduled dose. Concentrations drawn at other times may complicate interpretation of the result.

One particular strength of this study is the use of mexiletine in contemporary clinical practice, which allows the findings to be generalizable. The indication for mexiletine in the majority of patients in this study was for VT, which is consistent with modern practice. Furthermore, in modern clinical practice, mexiletine is typically used concomitantly with at least one other antiarrhythmic agent, which is supported by this study where mexiletine was used in conjunction with another agent in over 70% of patients. In earlier studies, mexiletine was often used as a single agent.

The study has several limitations. First, there are inherent limitations associated with a retrospective, chart review study design. It was often difficult to ascertain the reason for checking a concentration, as it is not always clearly documented in the medical record. In addition, it was sometimes challenging to determine when the level was checked in relation to the last dose, making it difficult to determine if the level corresponded to a peak, trough, or random concentration. Finally, establishing causality and, at times, an association between a medication and adverse event can be challenging in a retrospective study. The adverse events reported in this study may have been due to mexiletine, another medication, patients' comorbidities, or some other phenomenon not clearly documented in the patient record.

Conclusion

Serum mexiletine concentrations were often not drawn appropriately and often did not change the pharmacotherapy plan in the majority of patients. In contemporary practice, patients were maintained on lower serum concentrations with mexiletine primarily used as an adjunctive agent. A thoughtful approach to determining which patients would benefit from checking serum mexiletine levels is warranted. Patients with hepatic dysfunction had significantly higher mexiletine concentrations with similar dosing, but without further studies, the significance is unknown. Patients with hepatic dysfunction may benefit from therapeutic monitoring until further information is available. Additionally, patients who have concern of absorption may benefit from therapeutic monitoring to verify absorption. If a serum mexiletine concentration is checked, a trough concentration is preferred.

Acknowledgements

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from Mayo Clinic Institutional Review Board (IRB; no. 14-009225).

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Informed consent

Informed consent was not sought for this study because this research was not feasible without a waiver due to patients may have moved or were not reachable with current information. Given the infrequency of mexiletine levels, it was essential to include every patient for proper study powering. All data were stored/accessed on a secure network, and it was deemed minimal risk by IRB.

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