

Prevalence of Medications that may Induce QT Interval Prolongation in a Dental Clinic Population

Laura E Harris-Vieyra^{1*}, Kalin L Johnson² and Annika N Van der Werf³

¹Department of Periodontics, Creighton University School of Dentistry, Omaha, Nebraska, USA

²Department of Pharmacy Practice, Creighton University School of Pharmacy and Health Professions, Omaha, Nebraska, USA

³Department of Periodontics, Oregon Health & Science University School of Dentistry, Portland, Oregon, USA

*Corresponding Author: Laura E Harris-Vieyra, Department of Periodontics, Creighton University School of Dentistry, Omaha, Nebraska, USA.

Received: September 12, 2019; Published: September 30, 2019

Abstract

This retrospective study evaluates the prevalence of patients taking medications that may prolong the cardiovascular QT interval and determines which of these medications were taken most frequently by our sample dental clinic population. Clinical trials have confirmed that even small doses of epinephrine, acting as a vasoconstrictor in local anesthetic, can influence the functioning of the cardiovascular system and may lead to drug-induced QT interval prolongation in combination with certain medications. QT interval prolongation has been associated with torsades de pointes and sudden death. Medications of 500 adult patients were reviewed for a known drug-drug interaction with epinephrine. The data collected included sex, age, number of medications currently taken, and the list of current medications. The most commonly reported medications that may cause drug-induced QT interval prolongation, in our study population, were escitalopram and trazodone. One in ten patients of the study population reported taking at least one medication known to cause drug-induced QT interval prolongation. The drug-drug interaction between epinephrine and drugs that prolong the QT interval should be stressed to the dental team, to ensure they become aware of this potential interaction, risks, and possible complications of using vasoconstrictors in patients taking QT interval prolonging drugs. Alternatively, dentists and hygienists may wish to consider using 3% mepivacaine without epinephrine, rather than the more commonly used 2% lidocaine with epinephrine. Dental teams should be trained to acquire a complete and accurate medication history in order to fully evaluate for pertinent dental implications and drug-drug interactions.

Keywords: QT Interval; Epinephrine; Local Anesthetic; Dental; Medications; Drug Interactions

Abbreviations

OTC: Over the Counter; TCA: Tricyclic-Antidepressants

Introduction

Review of a patient's medication list is an important part of any dental visit. Medication history should include all prescription, over the counter (OTC), and herbal/supplement medications that the patient takes [1]. A study, showing a patient's perception of the importance of disclosing their medications to their dentist, found that 80.65% of patients always reported prescription medication, 71.43% always reported OTC medications, and 62.67% always reported herbal/supplement medications. When asked about the importance of informing

their dentist about their medications, 75.58% of patients believed that it was important to inform the dentist about prescription medications, 69.12% of patients believed that it was important to disclose over the counter medications, and 63.59% of patients believed that it was important to disclose herbals/supplements [2]. An estimated quarter of the population do not appreciate the importance of fully disclosing all medications, which may lead to unforeseen adverse reactions and drug interactions. This can make for a very dangerous situation for the patient.

Risks of using local anesthetics in combination with vasoconstrictors include cardiovascular events, drug interactions and allergic reactions [3]. Local anesthetics with vasoconstrictors may also adversely interact with tricyclic-antidepressants (TCAs) and fluoroquinolones. The mechanism of these adverse drug interactions with vasoconstrictors relates to the potential cardiovascular condition known as prolongation of the QT interval. The QT interval represents the measured interval between the beginning of the QRS complex to the end of the T wave [4]. The QRS complex and the T wave used to measure the QT interval are found on Electrocardiograms and show the atrial and ventricular depolarization and repolarization of the heart [5]. This QT interval represents the “time required for the heart to repolarize following the onset of depolarization” [6]. Prolongation of the QT interval can occur due to congenital reasons (genetic mutation) or acquired reasons (medication induced). “Drugs that prolong the QT interval may increase the risk of torsades de pointes, a potentially lethal ventricular arrhythmia” [7]. This is when the ventricles (lower chambers of the heart) beat abnormally and rapidly. Syncope (fainting) is the most common sign of torsades de pointes, which can progress to sudden death if normal rhythm is not restored in a timely manner [8]. Clinical trials have confirmed that even small doses of epinephrine, acting as a vasoconstrictor in local anesthetic, can influence the functioning of the cardiovascular system [9].

Lidocaine can be considered the most widely used local anesthetic in dentistry. The differences between most local anesthetics is in the onset of action and duration of the anesthesia achieved [10,11]. While most dentists might use lidocaine as the main anesthetic of choice, it is important to remember that vasoconstrictors are combined with local anesthetics to provide local hemostasis in the operative field and to delay their absorption. With dental anesthetics, the vasoconstrictor most often used is epinephrine, which can “prolong the duration of the anesthesia” [10]. It is important for dentists and dental hygienists, who administer local anesthetic, to know when their patient is taking medications that may interact with epinephrine and may lead to drug-induced QT interval prolongation. A decision about whether to proceed with the use of an anesthetic containing epinephrine will need to be made using the provider’s best clinical judgment. Patients at higher risk for QT interval prolongation are the elderly, women, patients with advanced heart disease, patients with a family history of sudden death, and patients taking drugs that prolong the QT interval [8].

Purpose of the Study

The purpose of this study was to evaluate the prevalence of patients taking medications that can prolong the QT interval and determine which of these medications were taken most frequently in our sample dental clinic population.

Materials and Methods

The Creighton University Biomedical Institutional Review Board granted exemption status to this study (#724323). A sample of 500 consecutively treated adults (aged 19-89) who had a recent dental periodic exam served as the study population. The list of patients was supplied by the Dental Information Technology Department via a data search in the electronic health record system (Axium). Each patient’s record was reviewed, and the data recorded. The data collected included sex, age, number of medications currently taken, and the list of current medications. Using the Dental School’s Electronic Drug Book, Lexicomp Online for Dentistry, a search for each medication was conducted to find medications which had a “Local Anesthetic/Vasoconstrictor Precaution” [12]. This precaution states that the medication was “one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes” [12]. These medications were flagged for a drug-drug interaction with epinephrine. Data was recorded with no personal identifiers retained after the data sheets were completed. Descriptive analysis and chi-square tests were performed.

Results

The records of 500 patients were evaluated. The sex distribution was 45.4% (227) male and 54.6% (273) female. The age range was 19-86 years old with a mean age of 55.22 years. The total number of medications taken by each patient ranged from 0-43, while the number of medications that have a risk for QT interval prolongation by a single patient ranged from 0-3. There were twenty different medications reported by the study population that could potentially cause drug-induced QT interval prolongation. These medications are listed in Table 1. Females reported an average of 4.86 total medications, which was a statistically significant difference compared to males, who reported an average of 3.45 total medications ($p < 0.001$). Based on the patient's age and the number of medications reported, for each one-year increase in age, there was a 0.13 increase in the number of medications reported ($p < 0.001$). In this population, on average, one new medication is added to the total number of medications a patient takes, every 7 - 8 years. The number of total medications increased significantly as the number of medications that could prolong the QT interval increased ($p < 0.001$) and the linear trend is significant ($p < 0.001$). A total of 22.4% (112) of the study population reported no medications (Figure 1).

Patients taking medications

Additional statistics were completed for patients who reported taking at least one medication. Of the 388 patients who reported taking at least one medication, 42.5% (165) were males and 57.5% (223) were females. The age range of this group was 19 - 86 with a mean average of 58.19 years. The total number of different medications taken by a single patient ranged from 1 - 43, with an average of 5.44 medications. The number of medications reported with a risk for prolongation of the QT interval ranged from 0 - 3, with a mean average of 0.19 medications.

- | |
|-------------------|
| 1. Amiodarone |
| 2. Amitriptyline |
| 3. Azithromycin |
| 4. Citalopram |
| 5. Chlorpromazine |
| 6. Clomipramine |
| 7. Escitalopram |
| 8. Flecainide |
| 9. Fluoxetine |
| 10. Iloperidone |
| 11. Imipramine |
| 12. Levofloxacin |
| 13. Methadone |
| 14. Nortriptyline |
| 15. Ondansetron |
| 16. Propafenone |
| 17. Quetiapine |
| 18. Ranolazine |
| 19. Risperidone |
| 20. Trazodone |

Table 1: Medications reported by the study population that may prolong the QT interval.

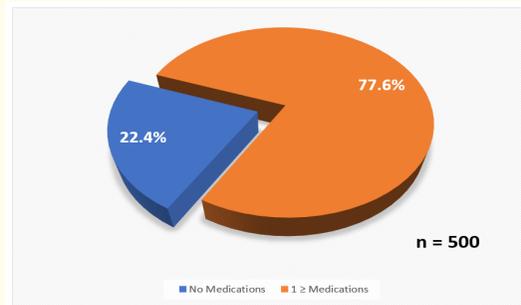


Figure 1: Percentage of patients reporting no medications and medications.

Patients reporting QT interval prolonging medications

Figure 2 lists the QT interval prolonging medications reported by patients and the number of patients taking each QT interval prolonging medication. A total of 39 patients took one QT interval prolonging medication and 15 patients took 2 - 3 QT interval prolonging medications. Among patients reporting one QT interval prolonging medication, escitalopram (23.1%) and trazodone (20.5%) were the most common medications implicated (Figure 2). Among patients reporting 2-3 QT interval prolonging medications, the combinations of citalopram and trazadone (20%) and escitalopram and trazadone (13.3%) were the most common medications implicated (Figure 3).

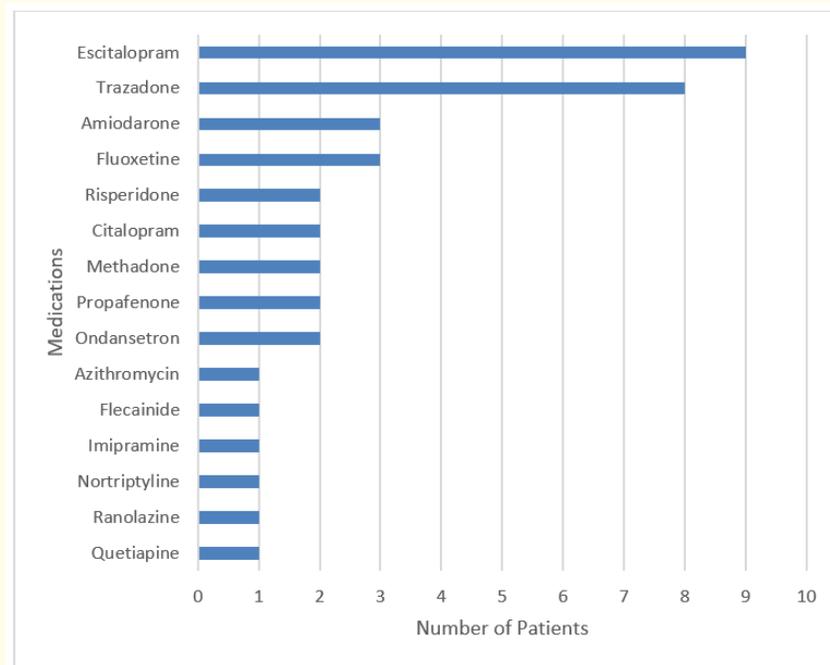


Figure 2: Prevalence of medications amongst patients reporting one QT interval prolonging medication.

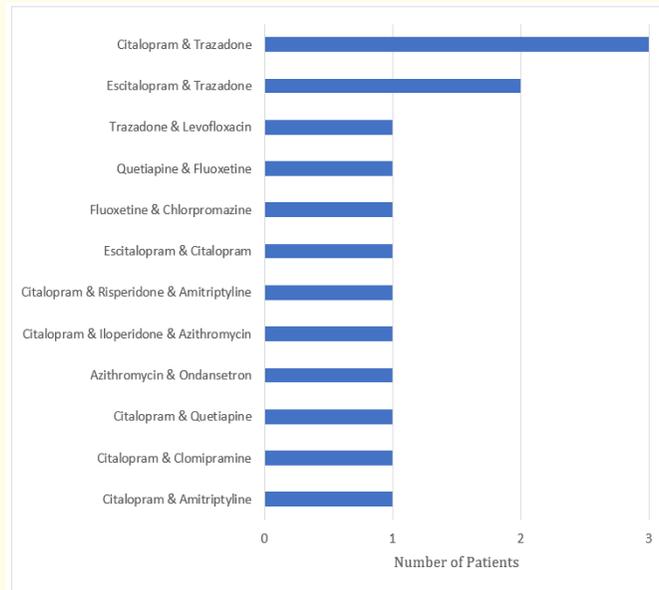


Figure 3: Prevalence of medications amongst patients reporting two or more QT interval prolonging medications.

Occurrence

A total of 54 patients, or 10.8% of the total study population (500), reported at least one medication that may prolong the QT interval (Figure 4). Of patients taking medications (388 patients reported at least one medication, Figure 5), 13.92% patients reported taking at least one medication that may prolong the QT interval. The difference in prevalence of QT interval prolonging medications when at least one medication was reported compared to the total study population was statistically significant (p-value = 0.029).

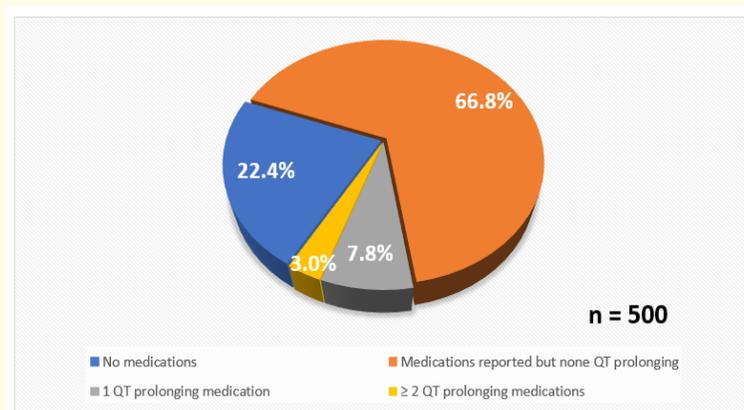


Figure 4: Presence of QT prolonging medications amongst total study population.

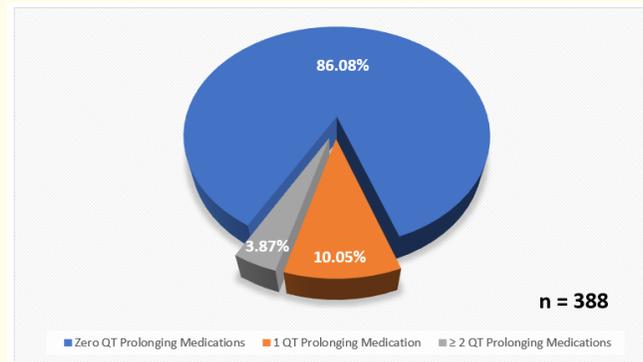


Figure 5: Presence of QT prolonging medication amongst patients reporting at least one medication.

Discussion

The Centers for Disease Control states that between 2011-2014, 48.9% of the United States population (including four age groups: under 18 years, 18 - 44 years, 45 - 64 years, and 65 years and over) have taken at least one prescription medication in the last 30 days. In addition, 23.1% of the United States population have taken three or more prescription medications and 11.9% have taken five or more prescription medications in the last 30 days [13]. While medications are imperative in treating acute and chronic conditions, their use comes with possible risks. Medications can cause adverse effects like constipation, dermatitis, diarrhea, dizziness, drowsiness, headache, insomnia, nausea, or xerostomia. Furthermore, medications may cause severe adverse effects such as organ damage, arrhythmias, and internal bleeding [14,15]. When multiple medications are taken concurrently, the potential for drug-drug interaction increases and should be evaluated by all providers, including dentists. These drug interactions may be synergistic or antagonistic in nature, affecting medication absorption, distribution metabolism, and excretion [16]. When multiple medications are taken that all cause the same adverse effect, a synergistic drug-drug interaction may occur and can amplify the presence and seriousness of the adverse effect.

Although the “risk of drug induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed” [12] it is important for dental providers to be aware of drug-induced QT prolongation and understand that the risk increases when the patient concomitantly takes other QT interval prolonging medications. This study demonstrates the prevalence of QT interval prolonging medications amongst patients in a University dental clinic setting. A total of 10.8% of the study population reported a medication that can cause drug-induced QT interval prolongation. Given this statistic and the common use of epinephrine in the dental setting, all dental providers should obtain a complete medication history from each patient and evaluate the patient’s risk for medication-induced QT prolongation.

This study found that escitalopram and trazodone were the two most common medications reported by patients implicated in the potential for drug-induced QT interval prolongation. Historically, antiarrhythmic agents were the first medications to be associated with drug-induced QT interval prolongation and ventricular arrhythmias. Subsequently, many non-cardiac medications have demonstrated the potential for inducing arrhythmias [6]. This study population displayed a high prevalence of non-cardiac medications with the potential for drug-induced QT interval prolongation. Many of these non-cardiac medications are indicated for treatment of psychiatric conditions, including escitalopram and trazodone, the two most commonly reported medications. Additionally, half of the medications listed in Table 1 are indicated for psychiatric conditions.

“Local anesthesia plays an important role in dentistry” [17]. While the most commonly used local anesthetic is lidocaine, this may not be the best practice for patients taking certain medications as part of their daily regimen. Lidocaine used for dental anesthesia is

combined with the vasoconstrictor epinephrine to extend the duration of the local anesthetic [17]. Local anesthetic with lidocaine and epinephrine is unlikely to lead to drug-drug interaction with local infiltration. However, because 15.3% of the anesthetic goes into the vascular space in the pterygomandibular region during an inferior alveolar nerve block injection, it behooves the dentist to aspirate before injecting the anesthetic [18]. In Lexicomp, the precautions for medications with a classification of “Clinical Risk Related to Drugs Prolonging QT Interval” explains, “In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that they be used with caution” [12]. An anesthetic option that can be considered by the dental provider for patients who report taking medications that may prolong the QT interval would be 3% mepivacaine without epinephrine, which has a rapid onset of action and a recommended dosage similar to lidocaine. After consulting the patient’s physician, limiting the epinephrine dose, or eliminating the epinephrine entirely, can allow the dentist to treat the patient with increased safety and comfort [11].

In deciding whether to utilize epinephrine or other medications that may prolong the QT interval, the dental provider should evaluate the patient’s risk factors for QT interval prolongation. As previously mentioned, these include the elderly, women, patients with advanced heart disease, patients with a family history of sudden death, and patients taking drugs that prolong the QT interval. [8] A thorough evaluation of the patient’s medication list for medications implicated in drug-induced QT interval prolongation is recommended (i.e. clarithromycin, erythromycin and ketoconazole are commonly implicated). If treatment with epinephrine is deemed necessary, the dental provider should monitor the patient for and ask them to report any signs of palpitations or syncope [8].

This study did have limitations. Medications obtained from a patient’s medical histories were all self-reported. The patients may not have correctly recalled active medications, may not have reported all medications or may not have been adherent to the medications listed. Medication omissions by patients are multifactorial and may arise from forgetfulness, not appreciating the importance of their dental provider being informed of their current medications, or not wanting the provider to know this aspect of their health history [2].

Conclusion

This study demonstrated that 10.8%, or one in ten patients, of the study population reported at least one medication known to cause drug-induced QT interval prolongation. When considering patients taking at least one medication, the percentage of relevant medications that may prolong the QT interval increased to 13.92%. The most commonly reported medications that may cause drug-induced QT interval prolongation were escitalopram and trazodone. These medications may pose a risk to the dental patient when combined with the vasoconstrictor epinephrine. This drug-drug interaction should be stressed to the dental team so that they may become aware of this interaction, the risks, and complications of using vasoconstrictors in patients taking QT interval prolonging drugs. They should be trained to acquire a complete and accurate medication history in order to fully evaluate the list for pertinent dental implications and interactions. As always, the goal of the dental team is to minimize patient risk during a procedure. This study highlights the prevalence of one important drug-drug interaction that the dentist and hygienist must evaluate for, in order to avoid serious consequences.

Conflict of Interest

The authors do not have any potential conflict of interest relevant to the present article.

Bibliography

1. Stefanac SJ and Nesbit SP. “Diagnosis and treatment planning in dentistry”. 3rd edition. St. Louis: Elsevier (2017).
2. Johnson KL, et al. “A Survey of Dental Patient Attitudes on the Likelihood and Perceived Importance of Disclosing Daily Medications”. *Journal of Dental Education* 82.8 (2018): 839-847.
3. Yagiela JA. “Adverse drug interactions in dental practice: Interactions associated with vasoconstrictors”. *Journal of the American Dental Association* 130.5 (1999): 701-709.

4. Garson A Jr. "How to measure the QT interval--What is normal?" *American Journal of Cardiology* 72.6 (1993): B14-B16.
5. Al-Khatib SM, *et al.* "What clinicians should know about the QT interval". *Journal of the American Medical Association* 289.16 (2003): 2120-2127.
6. US Pharmacist. "Drug-induced QT prolongation" (2007).
7. Botstein P. "Is QT interval prolongation harmful? A regulatory perspective". *American Journal of Cardiology* 72.6 (1993): 50B-52B.
8. Roden DM. "Drug-induced prolongation of the QT interval". *New England Journal of Medicine* 350.10 (2004): 1013-1022.
9. Dionne RA, *et al.* "Effects of diazepam premedication and epinephrine-containing local anesthetic on cardiovascular and plasma catecholamine responses to oral surgery". *Anesthesia and Analgesia* 63.7 (1984): 640-646.
10. Becker DE and Reed KL. "Essentials of local anesthetic pharmacology". *Anesthesia Progress* 53.3 (2006): 98-108.
11. Becker DE and Reed KL. "Local Anesthetics: Review of Pharmacological Considerations". *Anesthesia Progress* 59.2 (2012): 90-102.
12. Lexicomp Online for Dentistry (2018).
13. National Center for Health Statistics. "Therapeutic Drug Use, Centers for Disease Control and Prevention" (2017).
14. Moore PA, *et al.* "Adverse drug interactions in dental practice. Professional and educational implications". *Journal of the American Dental Association* 130.1 (1999): 47-54.
15. Haas DA. "Adverse drug interactions in dental practice: interactions associated with analgesics, Part III in a series". *Journal of the American Dental Association* 130.3 (1999): 397-407.
16. Dawoud BES, *et al.* "Drug interactions in general dental practice - considerations for the general dental practitioner". *British Dental Journal* 216.1 (2014): 15-23.
17. Lee J, *et al.* "Dental anesthesia for patients with allergic reactions to lidocaine: two case reports". *Journal of Dental Anesthesia and Pain Medicine* 16.3 (2016): 209-212.
18. Zenouz AT, *et al.* "The Incidence of Intravascular Needle Entrance during Inferior Alveolar Nerve Block Injection". *Journal of Dental Research, Dental Clinics, Dental Prospects* 2.1 (2008): 38-41.

Volume 18 Issue 10 October 2019

©All rights reserved by Laura E Harris-Vieyra, *et al.*