Review of quinidine for the WHO Pediatric Model List

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1. This application has been prepared for the expressed purpose of removing quinidine from the WHO Pediatric Model List on the grounds that quinidine has not been shown to prolong life in the pediatric population, and that it has in fact been implicated with increased morbidity and the induction of fatal arrhythmias in the adult population. Furthermore, quinidine has the potential to interact with many of the most commonly used antibiotics and antifungals in the developing world, further increasing the risk of QT prolongation and possibly death. Because it has been shown to increase mortality in adults, quinidine should also be considered for removal from the overall Model List.

2. N/A

3. None

4. Quinidine sulfate

5. N/A

6. Quinidine is widely available.

7. This application has been prepared for the purpose of removing quinidine from the Pediatric Model List. Quinidine is the only Class IA antiarrhythmic on the Pediatric List, and therefore the author is not requesting that a class of drugs be removed. Please note that the author does not wish to imply anything about any other Class IA antiarrhythmic drug.

8. A PubMed search was conducted to look for reviews containing estimates of pediatric arrhythmia statistics. The search was conducted on March 21, 2008 using broad search terms (Pediatric AND arrhythmia) and limits (Humans, Review, English, Core clinical journals, All Child: 0-18.) Of the 47 resulting publications, only 1 (Doniger et al 2006) provided a comparison of arrhythmia statistics in the pediatric population. The review reported that 55.1 per 100,000 pediatric (children under 18) Emergency Department (ED) visits in 26 community hospital EDs in the US were for arrhythmias. Of those presenting with arrhythmias, 50% had sinus tachycardia, 13% had supraventricular tachycardia, 6% had bradycardia, and 4.6% had atrial fibrillation. Thus, the incidence of pediatric arrhythmias, even in the acutely ill population, is quite low.

9. The 2007 WHO Model List contains quinidine in the 200mg form in the Complementary List for the treatment of arrhythmias. The United States Food and Drug Administration (FDA) has not approved quinidine for use in the pediatric population. Though clinicians
do sometimes use quinidine off-label for pediatric patients, it was not listed as a first line-agent in a pair of peer reviewed reviews regarding the treatment of pediatric supraventricular tachycardias, the most common class of arrhythmias in children (Luedtke et al 1997a)(Luedtke et al 1997b.) Thus, quinidine’s safety and utility is in question.

10. A PubMed search was conducted to look for studies that demonstrate if quinidine (or other Class IA antiarrhythmics) is associated with reduced mortality in the pediatric population. The search was conducted on January 21, 2008 using broad search terms (quinidine OR procainamide OR disopyramide AND arrhythmia) and limits (Humans, Clinical trials, Practice Guidelines, Randomized Controlled Trial, Review, All Child:0-18.) None of the 76 resulting publications were randomized trials evaluating the use of Class IA antiarrhythmics in the pediatric population. One publication (Gaita et al 2004) suggests that quinidine is effective in the treatment of short QT syndrome, though this regimen was only tested on one child. None of the publications discussed mortality as a primary endpoint, and so any lifesaving benefit of quinidine (and other Class IA antiarrhythmics) in the pediatric population has yet to be documented. No trials discussed adverse effects specifically in the pediatric population. However, the author is unaware of any evidence that would suggest that quinidine would lead to different side effects in the pediatric and adult populations. The lack of extensive use of quinidine in the pediatric population may explain the lack of data.

Due to the lack of published data on the pediatric population, adult data was consulted. One of the most common uses of quinidine is in the treatment of atrial fibrillation. A recent Cochrane meta-analysis (Lafuente-Lafuente et al 2007) reviewed the efficacy of various anti-arrhythmics in maintaining sinus rhythm after cardioversion for atrial fibrillation in adults (16 years old or greater.) The review included 45 randomized control trials (n = 12,559, mean participant age 69, SD 8 years) that evaluated any antiarrhythmic against a placebo, no treatment, or another drug, in adults with non-postoperative atrial fibrillation. It was found that antiarrhythmics as a group were able to significantly reduce atrial fibrillation recurrence (OR 0.19 to 0.60.) Class IA drugs (disopyramide and quinidine) however, were associated with an increase in mortality compared to controls (OR 2.39, 95% CI 1.03 to 5.59, P = 0.04.)

The AFFIRM Investigators (2002) found that in anticoagulated patients with atrial fibrillation, rate control with β-blockers or calcium channel blockers (diltiazem and verapamil) offered the same mortality rate as rhythm control using class I and Class III antiarrhythmics. The study included 4,060 patients (mean age 69.7 years, SD = 9.0 years.) The five year mortality for rate and rhythm controlled groups was 21.3% and 23.8% respectively (hazard ratio 1.15, 95% CI = 0.99 to 1.34.) Additionally, rhythm controlled patients were statistically more likely to have deleterious drug reactions (Torsade de Pointes in 0.2% vs. 0.8%, P = 0.007) and hospitalizations compared to the rate controlled patients (80.1% vs. 73.0%, P = <0.001.)
Thus, though quinidine may provide effective suppression of atrial fibrillation, it does not decrease mortality when compared to placebo (Lafuente-Lafuente et al 2007) or other safer therapeutic options (Lafuente-Lafuente et al 2007) (AFFIRM Investigators 2002.)

11. Quinidine has powerful anti-arrhythmic properties due to its ability to inhibit Na⁺ and K⁺ channels on cardiac myocytes (Roden et al 2006.) The K⁺ channel inhibition delays repolarization, thereby prolonging the QT interval, predisposing 2-8% of patients to Torsade de Pointes (TdP,) a potentially fatal arrhythmia (Roden et al 2006.) Particularly alarming is the fact that TdP can be induced at therapeutic and sub-therapeutic serum levels, and in instances without marked QT prolongation (Roden et al 1986.)

In fact, the AFFIRM trial mentioned in (10) found that a statistically greater number of patients in the rhythm control group experienced TdP (AFFIRM Investigators 2002.)

The risks associated with quinidine use also need to be examined in the context of polypharmacy in the developing world, where many of the most commonly used drugs are anti-infectives. Many antibiotics (ciprofloxacin, erythromycin, clarithromycin) and antifungals (fluconazole, itraconazole, ketoconazole) are inhibitors of CYP 3A4, one of the enzymes responsible for metabolism of quinidine (Kao 2005.) Thus, there is abundant potential for drug interactions to result in lethal increases in serum quinidine levels, especially in the hands of inexperienced clinicians.

In addition, quinidine is an inhibitor of CYP 2D6, and thus its use would lead to increased levels of any concurrently used drugs that are metabolized by this enzyme

12. N/A
13. Quinidine is widely available in generic form.
14. N/A
15. Quinidine should be removed from the Model list; all quinidine references should be removed from the Model Formulary.

Resources


