Reviewer No. 2 check list for application for deletion of QUINIDINE

The proposal to remove QUINIDINE from the EML is due to its lack of efficacy in prolonging life of cardiac patients. Furthermore this recommendation is based on its association with increased morbidity, risk of QT prolongation and induction of fatal arrhythmias in the adult population. Additionally, quinidine has the potential to interact with many of the most commonly used antibiotics and antifungals in the developing world. The drug has been included in the EML list under subsection 12.2: Antiarrhythmic medicines.

On the evidence given, the Committee should delete QUINIDINE

(1) **What is the reason for proposed deletion?**

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<td>Lack of efficacy</td>
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<td>Better alternative on, or to be added to Model List</td>
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(2) **If other, please describe.**

(3) **Is the evidence in the application adequate to support the recommendation?**

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(4) **What action do you propose for the Committee to take?**

I propose the deletion of QUINIDINE from the next WHO Model Essential Medicines List

(5) **Additional comments, if any.**

There was a note in the 15th edition of WHO EML (p.16): “This subsection will be reviewed at the next meeting of the Expert Committee”. According to this and to the evidence presented in the application, as well as in my short review (see below), I propose a possible fast-track deletion of procainamide, also a Class IA agent. I notice that in the 2005 Expert Committee Report the use of procainamide for treatment of arrhythmias was already questioned. The 2005 Expert Committee recommended a “fully review at the Expert Committee Meeting in 2007, including full applications for amiodarone and sotalol”.

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QUINIDINE SHORT REVIEW – MARCH 2009

APPLICATION

Drs. Daniel Friedman and Marcus Reidenberg, from the Weill Medical College of Cornell University, New York, USA, have submitted the application for the removal of quinidine from the 16th WHO EML. The purpose of removing quinidine is based on lack of efficacy in prolonging life of cardiac patients and, furthermore, is based on its association with increased morbidity, risk of QT prolongation and induction of fatal arrhythmias in the adult population. Additionally, quinidine has the potential to interact with many of the most commonly used antibiotics and antifungals in the developing world.

BACKGROUND

Nowadays antiarrhythmic agents have given place to physical methods for the management of some cardiac arrhythmias. This scenario is reinforced by the fact that antiarrhythmic agents not only help to control arrhythmias but also cause them (proarrhythmic effect), especially during long-term therapy. Thus, rational prescribing of those medicines requires two conditions: belief that the therapy will be beneficial and the risks of the chosen medicine can be minimized.

When antiarrhythmic agents are indicated, there is concern about proarrhythmic effect that occurred in 5-15% of patients, inducing arrhythmias more severe than the former ones. Among different agents, class I representatives present the highest arrhythmogenic potential. So, the use of these agents depends on the balance between their therapeutic effects and induced-arrhythmias risk.

Quinidine is an antiarrhythmic agent classified as Na+ channel blocker with a rate of recovery from drug-induced block around 3 seconds (Class IA). This action, as well as its vagolytic properties, is important in mediating the clinical effects of quinidine. Quinidine increases threshold for excitability and decreases automaticity and conduction, altering the re-entrant circuit. Quinidine prolongs refractoriness in most tissues. Conduction slowing owing to Na+ channel blockage may exacerbate re-entry. Induced arrhythmias are especially common during long-term treatment with quinidine, can be difficult to manage, and deaths due to intractable drug-induced ventricular tachycardia have been reported.2

COMMENTS

Effectiveness

Quinidine has been indicated for terminating a symptomatic ongoing arrhythmia or preventing recurrence of such arrhythmia (chronic therapy). However, chronic therapy is associated with higher risks.2

Quinidine is used to maintain sinus rhythm in patients with atrial fibrillation or atrial flutter and to prevent recurrence of ventricular tachycardia or ventricular fibrillation. However, the current treatment of choice is either amiodarone, beta-blockers, calcium-channel blockers or physical methods.

In this short review, relevant clinical outcomes, such as survival and morbidity, will be analyzed.

Comparisons among different strategies or different antiarrhythmic agents in atrial fibrillation

A large, randomized and multicenter trial (AFFIRM)3 compared long-term use of two treatment strategies: "rhythm-control" approach (cardioversion + anticoagulants +
antiarrhythmics - class I and class III antiarrhythmics, mainly amiodarone and sotalol) to maintain sinus rhythm; or “rate-control” strategy (atrioventricular nodal blocking agents – digoxin, beta-blockers and calcium-channel blockers - or ablation of the atrioventricular junction and pacemaker implantation, allowing atrial fibrillation to persist + anticoagulants) in patients with atrial fibrillation. The primary end point was overall mortality. There was no difference related to survival between both therapeutic strategies (356 vs. 310 deaths; 23.8% vs. and 21.3% mortality at five years; HR: 1.15 [95%CI: 0.99-1.34]; P=0.08), respectively in patients assigned to rhythm-control therapy and those assigned to rate-control therapy. So, this study found the same partial efficacy among beta-blockers or calcium-channel blockers (diltiazem and verapamil) compared with class IA (quinidine, disopyramide, procainamide), class IC (flecainide, propafenone) and class III antiarrhythmics (amiodarone, sotalol) in anticoagulated patients with atrial fibrillation.

Another trial4 randomly assigned 522 patients who had persistent atrial fibrillation after a previous electrical cardioversion to receive treatment aimed at rate control (oral anticoagulants + rate-slowing medication - digitalis, a calcium-channel blocker, and a beta-blocker, alone or in combination) or rhythm control (oral anticoagulants + sotalol, flecainide, propafenone or amiodarone). The end point was a composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, implantation of a pacemaker, and severe adverse effects of drugs. The primary end point occurred in 44 patients (17.2%) in the rate-control group and in 60 (22.6%) in the rhythm-control group. The distribution of the various components of the primary end point was similar in the rate-control and rhythm-control groups. Rate control was not inferior to rhythm control for the prevention of death and morbidity from cardiovascular causes in patients with a recurrence of persistent atrial fibrillation after electrical cardioversion. Even though this study had not used quinidine, it suggested the possibility that different antiarrhythmics could be switched in atrial fibrillation management.

A previous randomized trial (PIAF)5 (n=252 patients with symptomatic persistent atrial fibrillation) compared pharmacological cardioversion using oral amiodarone or rate control using diltiazem. There was no significant difference between the two groups. 60.8% of patients in the rate-control group and 55.1% in rhythm-control group (P=0.317) reported an improvement in their symptoms. There was no difference between the two groups related to quality of life that improved throughout the study. Once more, the same partial efficacy was showed with two different antiarrhythmics.

A Cochrane review6 pooled the data of studies AFFIRM6 and PIAF5. Concerning mortality, the systematic review reveals a non-significant relative risk of 1.14 (95% CI: 1.00 -1.31; P=0.06) in favor of rate control. The available data suggest that pharmacological cardioversion of atrial fibrillation is not superior to rate control and that particularly in older patients with significant comorbidity a strategy of rate control is a highly acceptable primary strategy. The available data cannot however be generalized to younger patients with new onset atrial fibrillation and in the absence of risk factors for stroke, those with structurally normal hearts or those with paroxysmal atrial fibrillation.

A Cochrane systematic review7 of 45 trials (12,559 adults with non-postoperative atrial fibrillation) was performed to determine the effect of long-term treatment with different antiarrhythmic agents on death, stroke, embolisms, adverse effects, pro-arrhythmia, and atrial fibrillation recurrence after restoration of normal sinus rhythm. Several class IA (disopyramide, quinidine), class IC (flecainide, propafenone), and class III (amiodarone,
dofetilide, sotalol) antiarrhythmics significantly reduced recurrent atrial fibrillation (OR: 0.19-0.60; NNT= 2-9).

Safety
The pharmacological management of arrhythmias requires careful consideration from a safety perspective. The foremost safety issue for antiarrhythmics is the propensity of class IA and class III agents to cause *torsades de pointes* arrhythmias. Class IA drugs, particularly quinidine, can induce *torsades de pointes* at low or subtherapeutic doses, but higher doses are not necessarily associated with an increased incidence. Quinidine has been associated with an increased risk for sudden death due to ventricular dysrhythmias.

Quinidine and procainamide have the highest potential to cause Q–T interval prolongation, because repolarization effects are a mechanism of their therapeutic efficacy. Prolongation of QT interval and *torsades de pointes* occur even at therapeutic plasma concentrations. A small study suggested that Korean subjects were less sensitive to quinidine-induced QT prolongation than Caucasian subjects, and that this trend was particularly true for females, not due to sex differences in quinidine pharmacokinetics, thus to a pharmacodynamic difference.

Quinidine syncope was reported in patients undergoing quinidine therapy for atrial arrhythmias. These patients manifested repeated episodes of ventricular arrhythmias as well as syncope during therapeutic use of quinidine.

Quinidine is contraindicated in patients with prolonged QT interval due to other causes and with heart failure exacerbation.

Diarrhea is the most common adverse effect during quinidine therapy, occurring in 30-50% of patients. Diarrhea-induced hypokalemia may potentiate *torsades de pointes* due to quinidine. Quinidine can induce thrombocytopenia which can be severe. Cinchonism (tinnitus and headache) can be produced when there are elevated plasma quinidine concentrations.

Another aspect that complicates antiarrhythmic therapy concerns drug interactions resulting in Q–T prolongation or TdP. Drug interactions are a significant safety issue in the management of atrial fibrillation. Those may be pharmacodynamic (concomitant use of medicines that prolong the QT interval), pharmacokinetic (quinidine interference with the metabolism of another drug), or both.

With regard to pharmacodynamic interactions, a wide range of medicines may prolong the QT interval and indeed may cause *torsades de pointes* directly. These included prokinetics (cisapride), antibiotics (macrolides, fluoroquinolones), antifungals (ketoconazole, fluconazole), HIV agents (indinavir, ritonavir, amprenavir, saquinavir), antihistamines (terfenadine, astemizole, diphenhydramine), calcium channel blockers (diltiazem, verapamil), psychiatric medicines (amitriptyline, desipramine, imipramine, clomipramine, fluoxetine, fluvoxamine, sertraline, lithium, thioridazine, chlorpromazine, haloperidol, methadone), in therapeutic doses or in overdose.

Quinidine is a potent inhibitor of hepatic cytochrome p450 (particularly CYP 3A4). Other drugs processed by the same system can block metabolism of quinidine and raise its plasma levels, increasing the risk of proarrrhythmia. Quinidine inhibits the metabolism of digoxin, codeine and tricyclic antidepressants, whereas its own metabolism is inhibited by a variety of agents including calcium antagonists, azole antifungals and cimetidine.
Comparisons among different strategies or different antiarrhythmic agents in atrial fibrillation

In the AFFIRM trial\textsuperscript{3}, “rate-control” strategy was associated with lower risk of adverse drug effects and fewer hospitalizations. The lack of benefit seen with rhythm control may well be due to the adverse side effect profile of the antiarrhythmics used (which resulted in increased hospitalization and drug withdrawal due to adverse events). The main concern associated with these medicines is their proarrhythmic potential. So, this study found that in anticoagulated patients with atrial fibrillation the use of beta-blockers or calcium-channel blockers (diltiazem and verapamil) showed lesser morbidity in comparison with class IA (quinidine included), class IB and class III antiarrhythmics.

In another study\textsuperscript{4} that compared rate control and rhythm control in patients with recurrent persistent atrial fibrillation, eight patients in each group died suddenly; 2 of the 16 were taking amiodarone, 1 was taking sotalol, and 1 was taking flecainide. Severe adverse effects of antiarrhythmic agents occurred mainly in the rhythm-control group: seven patients had the sick sinus syndrome or atrioventricular block; three had torsades de pointes or ventricular fibrillation; one had rapid, hemodynamically significant atrioventricular conduction during flutter; and one had drug-induced heart failure. The four patients who died suddenly while taking antiarrhythmic drugs were not counted separately, since it could not be proved that the death was related to the drug. In the rate-control group, there were only two patients with nonlethal digitalis intoxication. A pacemaker was implanted in three patients in the rate-control group (after atrioventricular-node ablation) and in eight patients in the rhythm-control group (for bradycardia during atrial fibrillation in one, after atrioventricular-node ablation in two, and for the sick sinus syndrome unmasked by cardioversion in five).

In PIAF trial\textsuperscript{5} that compared pharmacological cardioversion (oral amiodarone) or rate control (diltiazem), there were significantly more hospital admissions in rhythm-control group (69%) while only 24% were admitted in the rate control group ($P=0.001$). During follow up two patients in each group died. The frequency of drug side effects (64% versus 47%; $P = 0.011$) and rates of drug withdrawal (25% versus 14%; $P = 0.036$) were higher in the amiodarone group. There were no reports of amiodarone-associated proarrhythmic effects.

In the Cochrane\textsuperscript{6} review previously mentioned, both studies (AFFIRM and PIAF) showed a significantly higher hospitalization rate in the rhythm control group of patients (RR = 1.16; 95%CI: 1.11 - 1.22; $P <0.00001$, for combining data). The significantly higher rate of hospitalization with rhythm control has, no doubt, major cost implications for a treatment whose efficacy is now questionable.

In a Cochrane systematic review\textsuperscript{7}, antiarrhythmics increased withdrawals due to adverse effects (NNH= 9-27) and all but amiodarone and propafenone increased proarrhythmia (NNH=17-119). Quinidine, compared with controls, showed a non-significant but clear trend to increase mortality (OR: 2.26; 95%CI: 0.93-5.45; $P = 0.07$). Class IA agents, pooled, were associated with increased mortality compared with controls (OR= 2.39; 95% CI: 1.03-5.59; $P = 0.04$; NNH= 109 patients treated for 1 year to have 1 excess death; 95%CI: 34-4895 patients). Other antiarrhythmics did not modify mortality.

Quinidine caused more withdrawals than the other class I drugs (OR: 2.25; 95%CI: 1.45-3.51; $P=0.0003$; NNH=9 patients needed to treat for 1 year to have 1 excess withdrawal from treatment) but not more proarrhythmia. Amiodarone was associated with significantly fewer withdrawals (OR: 0.52; 95%CI: 0.34-0.81; $P = 0.004$) and less proarrhythmic events (OR: 0.28; 95%CI: 0.13-0.59; $P=0.0007$) than combined class I drugs; results were not modified in the sensitivity analysis. Then, class IA representatives are as effective as the other tested antiarrhythmics in reducing atrial fibrillation recurrence, but comparatively have more adverse effects, including death.
CONCLUSION
1) Quinidine presents the same partial efficacy as other antiarrhythmic agents of different classes in reducing atrial fibrillation recurrence and controlling atrial and ventricular arrhythmias.
2) Quinidine shows more adverse effects, including sudden death, Q–T interval prolongation, induced arrhythmias (torsades de pointes), syncope, diarrhea, thrombocytopenia, cinchonism. Compared with controls, quinidine showed a non-significant but clear trend to increase mortality. These adverse effects account for more hospitalizations and therapy withdrawals.
3) Beta-blockers, calcium-channel blockers and amiodarone represent safer substitutes to quinidine since they do not modify mortality. In comparison with class IA representatives, amiodarone was associated with significantly fewer withdrawals and fewer proarrhythmic events. Non-pharmacologic approaches can also substitute quinidine, proving to be safer than quinidine.
4) Quinidine is contraindicated in patients with prolonged QT interval and heart failure exacerbation.
5) Quinidine has high potential for drug interactions, with consequent increase in risk of side effects.

RECOMMENDATION
Facing a partial rate of efficacy, a high incidence of side effects including prolonged QT interval and potentially fatal induced-arrhythmias, as well as an easy substitution by other safer therapeutic agents and strategies in appropriate cardiac conditions, I endorse the application and recommend the deletion of quinidine from the WHO Model List of Essential Medicines.

REFERENCES