Amiodarone and beta blockade - is the whole better than parts?

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Amiodarone and beta-blockers are the two most widely used antiarrhythmic drugs. Although these agents share similar properties, they also have distinct pharmacological, pharmacokinetic and electrophysiological differences. Recent data suggest that when these agents are given as a combination, a synergistic interaction can occur with a beneficial effect on clinical outcome. Although the exact nature of this interaction remains unknown, the individual characteristics of one agent may be protective under conditions, which may negate or prevent the other agent from being effective. The purpose of this article is to review some of the individual differences between these two drugs that may explain their synergistic interaction when combined. J Clin Basic Cardiol 2000; 3: 205–7.

**Key words:** amiodarone, beta-blockers, mortality

The last century has witnessed remarkable and significant progress in the field of pharmacological and non-pharmacological therapies in cardiac arrhythmology. Two outstanding pharmacological agents that have contributed to these advances are beta-blockers and amiodarone. In contrast to other antiarrhythmic agents, large-scale randomised and meta-analysis studies have shown that these agents can significantly reduce cardiac arrhythmic mortality [1–6]. Moreover, beta-blockers have been shown undisputedly to produce a substantial reduction in all cause mortality [7, 8] whilst amiodarone has a neutral effect [3, 4] except in meta-analysis when a small (13 %) but significant reduction of mortality has been noted [6]. Although these agents share similar properties, they also have distinct pharmacokinetic and electrophysiological differences. Recent data [9–11] suggest that when these agents are given as a combination, a synergistic interaction can occur with a beneficial effect on clinical outcome. Although the exact nature of this interaction remains unknown, the individual characteristics of one agent may be protective under conditions, which may negate or prevent the other agent from being effective. For instance, ischaemia protective under conditions, which may negate or prevent the other agent from being effective. For instance, ischaemia or high sympathetic activity has been shown to reduce several electrophysiological effects of class III agents [12, 13]. Adding a beta-blocker under these circumstances can not only reduce the degree of ischaemia and abolish the deleterious proarhythmic effects of increased sympathetic activity but also restore antiarhythmic efficacy.

**Pharmacology of Amiodarone**

Amiodarone has a complex pharmacological profile and can inhibit sodium, potassium (Ikr and Iks) and calcium currents (IcaL). Amiodarone has a greater inhibitory effect on Ikr channels than on Iks channels. Its major antiarrhythmic properties are thought to be related to prolongation of the action potential duration. Amiodarone also exerts an antiadrenergic effect by non competitively inhibiting alpha- and beta-receptors [14]. Unlike beta-blockers, amiodarone does not bind to the catecholamine recognition site of the beta-receptor and appears to induce a significant decrease in the number of beta-adrenoreceptors [15]. In addition, amiodarone also inhibits the coupling of beta-receptors with the regulatory unit of adenylate cyclase [16]. These properties combine to inhibit the stimulated activity of adenylate cyclase but not its basal activity. This effect is different from adreno-receptor beta-blockers, which can inhibit both basal and stimulated activities of adenylate cyclase [14]. Amiodarone can reduce the cardiac chronotropic and inotropic responses to glucagon, whilst beta-blockers (propranolol) cannot [17]. Therefore, amiodarone has independent, distinct anti-adrenergic properties over and above those of conventional beta-blockers, which may explain a beneficial interaction when one agent is working sub-optimally. For instance, long-term treatment with beta-blockers can induce a significant increase in the number of beta-adrenoreceptors, which may explain the hyperadrenergic state frequently observed following the sudden withdrawal of drug therapy [16]. The addition of amiodarone under these circumstances may attenuate this effect.

**Effects of Adrenergic Stimulation**

Hyperadrenergic states and ischaemia play an important role in the genesis of ventricular arrhythmias, especially in patients with impaired left ventricular function. Amongst other actions adrenergic stimulation can: (1) increase inward calcium currents, potentiating delayed after depolarisations; (2) influence the pacemaker current thereby increasing automaticity of cardiac cells; (3) augment the delayed rectifier potassium current (in particular the Iks component), shortening action potential duration and refractoriness; and (4) enhance the sodium inward current, reversing the effects of class I agents [18]. Beta-blockers antagonise these effects of adrenergic stimulation, have anti-ischaemic properties and can improve left ventricular dysfunction [19, 20]. In addition, beta-blockers can abolish the circadian variation of myocardial ischaemia and sudden cardiac death, as well as raise the threshold for ventricular fibrillation [18].

**Amiodarone and Beta-Blocker**

Experimental studies have shown that the effect of amiodarone on action potential duration is significantly reduced when co-administered with isoproterenol [13]. However, the prolongation of action potential duration still remains...
beta-blocker therapy were at greater risk of recurrent ischaemic events and recurrent reinfarctions. Indeed, retrospective analysis of the EMIAT trial showed a reduction in mortality when amiodarone was combined with a beta-blocker (7.2 % vs 19 %) [10].

Boutitie et al. [11] analysed the interaction of amiodarone and beta-blockers by merging EMIAT and CAMIAT databases. This recently published study showed a significant reduction in cardiac and arrhythmic death in patients who were taking both amiodarone and beta-blockers. Although all cause mortality was decreased, it did not reach statistical significance (Figure 2).

Post hoc analysis data from the Antiarrhythmics Versus Implantable Defibrillator Trial (AVID) showed that patients treated with beta-blockers were not associated with a reduction in the composite end point of death or recurrent arrhythmia in amiodarone or ICD treated patients [25]. However, this study was not powered to detect a small, but perhaps clinically relevant, effect from beta-blockade [25]. Therefore larger, randomised prospective studies are still needed to help confirm this interaction.

Clinical, electrophysiological studies have shown beneficial effects, by combining amiodarone and a beta-blocker for the treatment of sustained ventricular tachyarrhythmias [26–28]. Given the perceived increased risks of bradycardias or haemodynamic intolerance, these studies also confirmed the general safety and tolerability when these agents are combined, provided that a small dose of beta-blocker is used and the dose is slowly increased.

**Conclusion**

In summary, beta-adrenergic stimulation can markedly modulate the electrophysiological actions of antiarrhythmic agents and could create a milieu that is proarrhythmic. The independent pharmacological properties of beta-blockers and amiodarone can interact synergistically to protect, when either drug alone lacks an efficacious effect. Until the results of larger prospective randomised studies are available, the current clinical evidence of this beneficial interaction derived from concomitant medication at baseline showed a strong trend but a non-significant reduction (p = 0.06) in patients who received beta-blockers. Examination of non-arrhythmic cardiac deaths disclosed that more fatal reinfarctions and unknown deaths occurred in the amiodarone-treated group (9.7 % and 8.7 %, respectively) than in the placebo treated group (2.9 % and 3.9 %, respectively). A history of previous myocardial infarction significantly increased the risk of death (24 % vs 10 %, p < 0.0001) and only 44 % of amiodarone treated patients received concomitant beta-blocker therapy. It is therefore plausible to speculate that patients not receiving beta-blocker therapy were at greater risk of recurrent ischaemic events and recurrent reinfarctions. Indeed, retrospective
from post hoc analysis data, indicate that amiodarone should not replace a beta-blocker or vice versa, but where indicated, these agents should be prescribed together.

References


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