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EDITORIAL

Pleiotropic actions of amiodarone: still puzzling after half a century

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Amiodarone was developed in the early 1960s based on extracts from the Khella plant and was initially used as a coronary dilator for the treatment of angina pectoris (Singh 2008). In 1970, Singh and Vaughan Williams discovered that amiodarone also directly affected myocardial tissue, prolonging the cardiac action potential and protecting against ouabain-induced arrhythmias in guinea pigs (Singh and Vaughan Williams 1970). To date, amiodarone remains one of the most commonly prescribed antiarrhythmic drugs in clinical practice and is used in the treatment of both ventricular and supraventricular arrhythmias. In particular, amiodarone plays a major role in the maintenance of sinus rhythm in patients with atrial fibrillation (Heijman et al. 2013; Zimetbaum 2012).

The seminal Cardiac Arrhythmia Suppression and Survival Trial (CAST) and Survival with Oral D-Sotalol (SWORD) trial have highlighted the proarrhythmic risks of classes I and III antiarrhythmic drugs (Echt et al. 1991; Waldo et al. 1996). In contrast to many other antiarrhythmic drugs, amiodarone is generally not associated with drug-induced "torsades des pointes" arrhythmias or an increase in cardiovascular mortality compared to placebo (Singh 2008; Zimetbaum 2012). However, its clinical application is severely limited by its pronounced extra-cardiac toxicity. In particular, amiodarone has been associated with hepatic toxicity, manifesting as transaminase elevation, thyroid dysfunction, and pulmonary toxicity (Zimetbaum 2012). The latter is a major cause for discontinuation of amiodarone treatment and has an incidence between 5 and 13 %. Amiodarone-induced pulmonary toxicity can occur acutely (within weeks after the start of therapy), in which case it is most commonly characterized by acute pulmonary hypersensitivity with patchy infiltrates, or develop with chronic treatment as increased pulmonary interstitial fibrosis (Schwaiblmair et al. 2010; Zimetbaum 2012). It has been suggested that amiodarone's iodine moieties and extreme lipophilic character strongly contribute to its toxicity. In addition, these properties result in a long half-life, such that side effects may persist (or even develop) after amiodarone treatment has been halted (Papiris et al. 2010). The pronounced toxicity of amiodarone has prompted the development of the derivative dronedarone, which lacks the iodine moieties and is less lipophilic than amiodarone, resulting in a much shorter half-life, although accumulation in tissues still occurs (Dobrev and Nattel 2010). In the DIONYSOS trial, dronedarone indeed resulted in a lower incidence of adverse thyroid, neurologic, skin, and ocular effects in patients with atrial fibrillation compared to amiodarone, although it was also less effective (Dobrev and Nattel 2010). However, more recent investigations have suggested that dronedarone does not have a superior safety profile compared to other antiarrhythmic drugs for the treatment of atrial fibrillation (Chatterjee et al. 2012; Said et al. 2012). In addition, the PALLAS trial was recently halted due to excess mortality in the dronedarone-treated arm, raising concerns about the usefulness of dronedarone (Nattel 2011). Other amiodarone derivatives with improved water solubility (e.g., budiodarone) are being developed and have shown a promise as antiarrhythmic agents for both atrial and ventricular arrhythmias (Goegelein et al. 2011; Billman et al. 2012; Ezekowitz et al. 2012).

In the current issue of *Naunyn-Schmiedeberg's Archives of Pharmacology*, Polat et al. (2013) show that amiodarone has a protective effect on lung tissue in a rat model of cecal ligation

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and puncture (CLP)-induced sepsis, characterized by a systemic inflammatory response as a consequence of an infection. In this study, rats underwent CLP via an abdominal incision. Sham-operated rats also received laparotomy, and their ceca were manipulated but not ligated or punctured. Following the operation, rats received saline or low- or high-dose amiodarone (25 and 50 mg/kg, respectively). In the 16 h postsurgery, the CLP rats showed a strong inflammatory response, as indicated by increased serum levels of the inflammatory cytokines interleukin (IL)-1β, IL-6, and tumor necrosis factor alpha (TNF-α). In addition, lung tissue of CLP rats showed reduced levels of antioxidants (glutathione and superoxide dismutase) and increased 8-iso-prostaglandin F2α, indicating oxidative stress. Histopathological analysis of lung tissue from CLP rats revealed infiltration of inflammatory cells and necrotic regions. All of these pathological responses were significantly attenuated in a dose-dependent manner in rats treated with amiodarone (Polat et al. 2013). Interestingly, there was also a tendency towards a lower mortality over the 16-h follow-up period in the amiodarone-treated groups. These results suggest that amiodarone may exert remarkable protective effects in pulmonary tissue in this model, in agreement with a previous study from the same authors in rats with carrageenan-induced paw edema (Halici et al. 2007). This striking protective action clearly contrasts to the pulmonary toxicity frequently observed in patients.

This study raises several important questions. Besides potential species differences, these seemingly paradoxical results likely depend on differences in dose and duration of amiodarone treatment. Indeed, amiodarone maintenance doses of more than 500 mg/day have been shown to be more toxic than lower doses in the clinical setting, although pulmonary toxicity appears to develop with any dose (Papiris et al. 2010; Schwaiblmair et al. 2010). Moreover, in patients, there is an increased incidence of amiodarone-induced pulmonary toxicity with longer durations of treatment (Papiris et al. 2010; Schwaiblmair et al. 2010). In rats, the experimental animal of choice in the study by Polat et al. (2013), amiodarone has been associated with pulmonary toxicity after a period of several weeks (Reasor and Kacew 1996). Important contributing factors to amiodarone-induced pulmonary toxicity include direct cytotoxic effects (notably of *N*-desethylamiodarone, the main metabolite of amiodarone), phopholipidosis, immunological mechanisms, and activation of the angiotensin system (reviewed in Papiris et al. 2010; Reasor and Kacew 1996). However, the exact mechanisms contributing to amiodarone-induced pulmonary toxicity remain incompletely understood.

Many years of research on amiodarone's mechanisms of action has produced a complicated picture, showing a wide range of pleiotropic effects, both in the heart and elsewhere. Amiodarone and its active metabolite *N*-desethylamiodarone directly inhibit the cardiac Na^+ current (I_{Na}), a wide range of cardiac K^+ currents; the L-type Ca^{2+} current ($I_{Ca,L}$); and the hyperpolarization-activated "funny current" (I_f), resulting in a reduction of cardiac excitability and prolongation of cardiac repolarization (reviewed in Heijman et al. 2013). In addition, amiodarone is a non-competitive α- and β-adrenoceptor antagonist. The direct electrophysiological effects of amiodarone and its derivative dronedarone are more pronounced in the atria than ventricles, likely contributing to their success in the treatment of atrial fibrillation and low incidence of ventricular proarrhythmia (Bogdan et al. 2011; Dobrev et al. 2012; Ehrlich and Dobrev 2011; Schmidt et al. 2012).

In contrast to other antiarrhythmic drugs, amiodarone can prevent atrial fibrillation-promoting atrial electrical remodeling in a dog model of pacing-induced atrial tachycardia, thereby reducing the incidence and duration of atrial fibrillation (Shinagawa et al. 2003). It has been suggested that prevention of L-type Ca^{2+} current α_{1C}-subunit downregulation contributes to these anti-remodeling properties (Shinagawa et al. 2003). Similarly, amiodarone prevented both electrical and structural remodeling in the ventricles of canines with heart failure (Ashikaga et al. 2006) and in a rat model of inflammatory cardiomyopathy (Tachikawa et al. 2005). Of note, in the latter study, inflammatory markers IL-6 and TNF-α were unchanged in myocardial tissue by treatment with 50 mg/kg amiodarone for 6 weeks (Tachikawa et al. 2005), in contrast to short-term treatment in the sepsis model (Polat et al. 2013), further highlighting the complex actions of amiodarone and the importance of differences in treatment duration and/or pathology.

The antioxidant and anti-inflammatory actions of amiodarone observed in the present study by Polat et al. (2013) are consistent with its effects on IL-1β, IL-6, and TNF-α reported in human peripheral blood mononuclear cells after 24 h of culture in the presence of amiodarone (Matsumori et al. 1997), its effects in a mouse model of viral myocarditis (Ito et al. 2002), and its protective effects on canine ventricular myocytes during an acute challenge with H_2O_2 (Ide et al. 1999). However, chronic treatment with amiodarone (1 year) resulted in an increase in TNF-α in patients with ischemic cardiomyopathy, and no change in patients with nonischemic cardiomyopathy (Oral et al. 1999), again suggesting important differences between acute and long-term treatment.

Many additional effects of amiodarone have been described. For example, amiodarone and *N*-desethylamiodarone are also potent vasodilators, affecting Ca^{2+} handling in endothelial cells (Grossmann et al. 1998, 2000; Himmel et al. 2000). The high atrial rate during atrial fibrillation induces oxidative stress and microvascular flow abnormalities in ventricles (Goette et al. 2009), and the acute anti-inflammatory and vasodilatory properties of amiodarone could contribute to its antiarrhythmic efficacy. Amiodarone and dronedarone have also emerged as potential treatments for Chagas disease, a tropical parasitic disease which is also associated with

cardiovascular complications, notably dilated cardiomyopathy and associated arrhythmias (Benaim and Paniz Mondolfi 2012).

Taken together, these studies emphasize that half a century after its initial development, our mechanistic understanding of the pleiotropic actions of the most commonly prescribed antiarrhythmic drug is still incomplete. Although amiodarone at first glance appears to be an unlikely candidate for the protection of lung tissue during sepsis, given its well-known pulmonary toxicity, the work by Polat et al. (2013) shows that with the right dose and timing, the non-electrophysiological actions may still confer important antioxidant and anti-inflammatory benefits. It would be interesting to determine in future studies whether similar benefits can be observed when sepsis is already present (i.e., during treatment as opposed to prevention), and whether improved survival is maintained during longer follow-up periods. A better understanding of the pleiotropic actions of amiodarone, combined with more detailed information on pathology-specific disease mechanisms, will likely facilitate the development of new pharmacological agents that can exploit the desirable effects while reducing the number of unwanted side effects.

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Conflict of interest None.

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