Bisphosphonates and Cardiac Electrophysiology: Should the Red Flag Be Raised Higher?

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Edirorial Comment

Bisphosphonates are widely employed to decrease bone loss in disorders characterized by increased osteoclast-mediated bone resorption, such as senile osteoporosis.[1] Although generally well-tolerated, side effects such as an acute inflammatory phase reaction, osteonecrosis of the jaw, gastrointestinal disorders, or hypocalcemia have been described.[1] Also, contradictory reports of an association between atrial fibrillation (AF) and the use of bisphosphonates has led to confusing statements and sent mixed messages to practitioners and patients.[2] Details on these conflicting observations are summarized in previously published review articles.[1-3] Interestingly, several hypotheses linking bisphosphonates to the onset of AF have been formulated: an acute increase in proinflammatory cytokines, disturbances in calcium homeostasis, or extracellular matrix remodeling.[2] To date, however, none of these premises have been tested, the mechanisms by which bisphosphonates may impact cardiac electrophysiology are unknown, and as of late 2008, the Food and Drug Administration failed to identify a clear association and concluded that no change in prescribing practices was warranted.[1,2]

In this issue of the *Journal of Cardiovascular Electrophysiology*, Bonilla *et al*. present a multifaceted investigation describing plausible mechanisms for bisphosphonate-induced cardiac arrhythmias.[4] Their results have substantial mechanistic depth and, albeit provocative, put at question the previous status quo on an association between bisphosphonates and cardiac arrhythmias.

The authors started their work with a clinical observation compatible, although inconclusively, with a bisphosphonate-induced arrhythmia. A 55-year-old woman, having had a single dose of ibandronate—a commonly used bisphosphonate—experienced syncope and subsequently presented with QT/QTc interval prolongation, which normalized following ibandronate discontinuation. Based upon this suspicious observation, the authors conducted a comprehensive basic and translational investigation that included a 3-month treatment of canines with ibandronate, subsequent cell electrophysiology-patch-clamp and intracellular calcium measurements, and numerical simulations.

The authors demonstrate clearly that ibandronate exerts a massive effect on myocyte electrophysiology. First, the action potential duration (APD) is about 30–40% prolonged with early after depolarizations arising significantly more after ibandronate perfusion. Also, the authors noticeably show that the repolarizing current I_{to}, both slope conductance and maximal density, is reduced by ibandronate and that ibandronate-related APD changes are heavily dependent on the sarcoplasmic reticulum (SR) calcium-controlling receptor, the ryanodine receptor (RyR). When the RyR was blocked after ryanodine perfusion, or that the calcium was chelated with BAPTA, none of the APD changes described above were seen. Besides, ibandronate treatment caused a significant increase in calcium load and a decrease in calcium spark amplitude, while spark intensity was rebounding during washout. The latter observation could be an important insight as the proarrhythmic action may follow bisphosphonates withdrawal rather than associate with its use. Altogether, two seemingly independent mechanisms were probably at play: a decrease in repolarization reserve with a decreased I_{to} current, and RyR blocking action with increased SR load. In silico, an additional potentially critical finding was that the forward RyR inactivation rate may underlie bisphosphonate-related I_{to} current decrease and APD prolongation. Although the means by which the former is mechanistically related to the latter remain unclear, these original mechanisms are likely additive as both were needed to mimic experimental APD prolongation.

Hence, this well-conducted study yields solid evidence that ibandronate—and presumably other bisphosphonates—adversely modulate cardiac myocyte electrophysiology. Nonetheless, it is uncertain whether these findings translate to the organ or the in vivo realities. As pointed out by the authors, compensatory mechanisms such as intercellular communication, a modulation of the autonomic nervous input, or an increased inflammation could sum up to a much lesser effect that the one seen in isolated cells. Still, the work presented by Bonilla *et al*. stands as a compelling mechanistic dataset that helps in appreciating bisphosphonates' impact on cardiac electrophysiology. This effort warrants further investigation to clarify cellular mechanisms, and to assess whether atrial myocytes are similarly sensitive to bisphosphonates. Also, this work is a call for clinical studies focused on a detailed analysis of the time period following bisphosphonates withdrawal. Altogether, Bonilla *et al*.'s observations are a strong scholarly incentive for a comprehensive research program aiming at elucidating the effects of bisphosphonates on the heart.

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