

Evidence Accumulates Against Angiotensin-Converting Enzyme Inhibitors and Beta-Adrenergic Blockers as Important Co-factors for Anaphylactic Reactions



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Bradykinin is a 9-amino-acid peptide that is a very potent vasodilator. It stimulates production of nitric oxide and prostacyclin (PgI₂) by vascular endothelium, which dilate both resistance and conductance vessels. Found predominately in the pulmonary vascular endothelium and epithelium of the kidneys, it contracts nonvascular smooth muscle of the bronchi and gut, while increasing vascular permeability. Bradykinin is generated in the kinin-kallikrein system from its high-molecular-weight precursor kininogen, by the protease kallikrein. It is degraded in separate locations by angiotensin-converting enzyme (ACE), aminopeptidase P and carboxypeptidase N. It is recognized that bradykinin is hydrolyzed by ACE on a single “pass through” of the lungs.

Yet, radiographic contrast materials (RCM) can inhibit ACE,¹ and some patients who experience severe anaphylactic reactions from RCM have evidence of cleavage of the high-molecular-weight kininogen.² From the perspective of practical clinical advice in the 2020 manual on contrast media of the American College of Radiology, the section on pre-procedure considerations does not mention ACE inhibitors (ACE-I) or angiotensin receptor blockers (ARBs).³ For beta-blockers, the advice is: “Patients on beta-blocker therapy do not need to discontinue their medication(s) prior to contrast medium administration.”³ For patients with cardiac disease, the manual comments there may be an increased risk for patients with “severe cardiac disease...of a non-allergic cardiac event if an allergic-like or non-allergic contrast reaction occurs.” However, the advice is not to restrict the use of RCM or premedicate because of cardiac disease.³ The potential harms of ACE-I and beta-adrenergic blockers always have been important considerations for allergy-immunology specialists regarding anaphylaxis, asthma, skin

testing, and immunotherapy with aeroallergens and venoms. The benefits versus risks tradeoffs were reviewed thoughtfully by Coop et al in this journal in 2017.⁴ In this issue, in a case control study, Smith et al⁵ describe their review of 71,782 cardiac catheterizations with low-osmolality RCM at a single institution to explore if the concomitant administration of ACE-I or beta-adrenergic blockers was associated with increased numbers of anaphylactic reactions to RCM. Approximately 50% of patients were receiving beta-adrenergic blockers, and 37% of patients were being treated with ACE-I.⁵ There was no apparent increased risk in patients attributable to either or both medications so that the authors concluded that it was not necessary to discontinue these treatments before the cardiac catheterization.⁵ These findings extend the current literature from high- and low-osmolality RCM.^{6,7}

In patients receiving subcutaneous immunotherapy (SCIT), in a single center study where only systemic reactions for which epinephrine was administered were analyzed, there were 266 such reactions of which 20 (7.5%) occurred in patients using either ACE-I or ARBs.⁸ As controls, there were 246 reactions in patients not using either of these 2 classes of medications. The majority of reactions occurred during the build-up phase for all patients. Because the inclusion criteria required that all patients receive at least 1 injection of epinephrine, 7 of 20 (35%) ACE-I+ or ARB+ and 74 of 246 (30%) ACE-I– or ARB– were treated with a second injection of epinephrine.⁸ These rates were not significantly different. Time to resolution was similar at 22 and 24 minutes, respectively. The authors identified a significant difference between groups in the number of World Allergy Organization grade 3 and 4 reactions, 15% and 2%, respectively.⁸ How to act on this information where there are clear benefits for cardiovascular health and treatment of diabetes mellitus will require individual discussion with the patient and potentially other physicians and health care professionals. Reassuringly, Stoevesandt et al⁹ could not find any detrimental effects of cardiovascular medications in 71 patients using ACE-I and in 40 patients taking beta-adrenergic blockers, when focusing on reactions while receiving maintenance venom immunotherapy and from field stings. The latter occurred in 42.7% of patients resulting in objective immediate reactions in 7.3% of patients.⁹ As reviewed by Golden,¹⁰ the American Academy of Allergy Asthma and Immunology, American College of Allergy Asthma and Immunology, Joint Council of Allergy Asthma and Immunology,¹¹ and European Academy of Allergy Asthma and Immunology¹² practice parameters consider the benefits of venom immunotherapy more than potential harms in the presence of ACE-I and beta-adrenergic blockers.

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It is worth noting from a historic perspective that in 1990, Hepner et al.¹³ reported findings when testing whether beta-adrenergic blockers would increase the reaction rate to subcutaneously administered immunotherapy. From 56,105 injections in 3178 patients over 1 year, there were 166 systemic reactions in 144 (4.5%) patients.¹³ These data translated into 1 systemic reaction in 333 injections, with no increased risk in the 68 patients who were using beta-adrenergic blockers for the whole year as just a single patient had a reaction.¹³ It is my view that these data are a reasonable reference for comparison for our practices with 1 systemic reaction per 333 injections of SCIT. As potential new co-factors impacting the risk of anaphylaxis are proposed, the impact on systemic reactions from immunotherapy will be a real-time experiment to identify or exclude the novel interaction.

In studying the frequency and severity of anaphylaxis to identify attributable risks of ACE-I, ARBs, and beta-adrenergic blockers as potential co-factors, we must explore additional overlapping characteristics including increasing age and underlying coronary artery disease, valvular heart disease, congestive heart failure, and hypertension.¹⁴ Many patients take H1 antihistamines purposefully (and do not report this information to nurses) on the day of their aeroallergen or venom SCIT injections, even if the literature does not support their benefit to prevent anaphylaxis. Regarding patient care recommendations, the weight of information suggests continuing ACE-I, ARBs, and beta-adrenergic blockers in anticipation of either an intravenous or intra-arterial RCM procedure as well as venom immunotherapy and discussing the potential but unlikely harms in patients receiving aeroallergen SCIT.

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