

3. Romano A, Gaeta F, Valluzzi RL, et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of alternative cephalosporins. *J Allergy Clin Immunol*. 2015;136(3):685–691.e3.
4. Romano A, Valluzzi RL, Caruso C, Maggioletti M, Quarantino D, Gaeta F. Cross-reactivity and tolerability of cephalosporins in patients with IgE-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol Pract*. 2018;6(5):1662–1672.
5. Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy*. 2014;69(4):420–437.
6. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs: an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy*. 2013;68(6):702–712.
7. Tuyls S, Breyneart C, Schrijvers R. Subgroups in cephalosporin allergy, making a patient-tailored approach redundant? *J Allergy Clin Immunol*. 2016;137(1):331.
8. Saenz de San Pedro B, Mayorga C, Torres MJ, Florido JF, Quirarte J, Blanca M. Boosted IgE response after anaphylaxis reaction to cefuroxime with cross-reactivity with cefotaxime. *Ann Allergy Asthma Immunol*. 2002;89(1):101–103.

Mixed drug reaction to amiodarone characterized by sequential immediate, immune complex, and delayed hypersensitivity



Amiodarone is a class III antiarrhythmic agent indicated for the treatment of tachyarrhythmias and frequently used in the management of atrial fibrillation. Pulmonary, cardiac, thyroid, hepatic, ocular, and neurologic toxic effects caused by the accumulation of the drug in the tissue from long-term therapy attributable to its long half-life and lipid solubility have been previously described.¹ Phototoxic effects resulting from the accumulation of free oxygen radicals from radiation is a common complication of long-term therapy.¹ Hypersensitivity reactions, however, account for less than 1% of adverse effects.^{2–4} We describe a patient with an unusual hypersensitivity reaction to amiodarone that involved 3 sequential phases: acute anaphylaxis, followed by a type 3 serum sickness–like reaction, and finally, a delayed type 4 reaction that manifested as exfoliative dermatitis with eosinophilia.

An 81-year-old man was administered amiodarone for atrial fibrillation associated with atrial thrombosis for which rivaroxaban was administered more than 4 weeks ago. The patient has ischemic heart disease and received a coronary artery bypass graft 35 years ago with percutaneous angioplasty performed 10 years ago, which was complicated by stent occlusion. His cardiovascular disease was treated for several years with a regimen of isosorbide mononitrate, ramipril, atorvastatin, and ezetimibe. He had no history of type B (idiosyncratic responses that cannot be predicted from the known pharmacologic mechanisms of a drug) allergic reactions, iodine, or contrast reactions.

After 6 days of amiodarone therapy, anaphylaxis characterized by generalized urticaria, facial angioedema, wheezing, and chest pain developed in the patient. He was successfully treated with adrenaline and fexofenadine in the hospital, and his amiodarone therapy was ceased. His electrocardiogram revealed atrial fibrillation with no ischemic change. His chest radiograph revealed minor atelectasis of his left lung base. There was a short-term increase in his tryptase level to 6.8 $\mu\text{g/L}$ against a baseline of 2.8 $\mu\text{g/L}$.

Seven days after the administration of amiodarone, fever, polyarthralgia, and a diffuse purpuric rash accompanied by an elevated C-reactive protein level (280 mg/L) and hypocomplementemia (C3: 0.26 g/L; C4: 0.06 g/L) developed in the patient. Skin biopsy revealed leukocytoclasia and a perivascular eosinophilic infiltrate in the absence of other changes of vasculitis, such as fibrinoid necrosis or thrombosis. There was no detectable antinuclear antibody, antineutrophil cytoplasmic antibody, or cryoglobulin. IgG, IgA, and IgM levels were normal. Furthermore, HIV, hepatitis B, and hepatitis C serologic test results were negative, and the antistreptolysin titer was normal. Blood cultures, urinalysis, and respiratory viral swabs did not isolate a pathogen.

A tapering course of prednisone was commenced at 1 mg/kg daily. His fever, purpuric rash, and arthralgia resolved after 10 days of therapy. However, with a dose of prednisone at 0.7 mg/kg daily,

the following symptoms developed in the patient: a desquamating rash (Fig 1), mild erythroderma accompanied by eosinophilia (eosinophil count, $2.9 \times 10^9/\text{L}$), cervical lymphadenopathy, and mild transaminitis (alanine aminotransferase, 82 U/L [reference range, <55 U/L]; aspartate aminotransferase, 54 U/L [reference range, 12–34 U/L]). There was no recurrence of fever or arthralgia. His C-reactive protein and complement levels were normal, and human herpesvirus 6 DNA was not detected. Prednisone therapy was increased to 1 mg/kg daily and tapered during 6 weeks without recurrence of hypersensitivity. His atrial fibrillation was subsequently treated with diltiazem. The patient did not experience pulmonary or thyroid toxic effects during follow-up.

Basophil activation testing (BAT) was performed to amiodarone and the excipient povidone per our previously published protocol.⁵ Interferon gamma release assays and bromide uridine enzyme-linked immunosorbent assays were performed to determine in vitro stimulation and proliferation of the patient's lymphocytes to amiodarone, but the results of these studies were negative.⁶

Hypersensitivity reactions to short-term use of amiodarone are rare and have been sparsely described in the literature. Our case is unique because our patient's reaction comprised multiple immunologic mechanisms (types 1, 3, and 4 Gell and Coombs reactions), which may be termed a *mixed drug reaction* according to the Joint Task Force on Practice Parameters.⁷ This type of reaction is not described in any other practice parameter. We did not find another case report of a mixed drug reaction in the literature.

Our patient had a type 1 hypersensitivity reaction demonstrated by urticaria, angioedema, and wheezing with significant dynamic change in serum mast cell tryptase. In addition, BAT supported an immediate hypersensitivity reaction to amiodarone (Fig 1), and this is the first report, to the best of our knowledge, of a positive BAT result to the drug in a case of anaphylaxis after the administration of the oral formulation.⁸ Excipients within the oral amiodarone formulation include iodine (povidone), maize starch, lactose, magnesium stearate, and anhydrous colloidal silica. Moreover, BAT was performed to iodine (povidone) because it is an excipient and has been reported rarely (<1%) to be an allergen in patients with amiodarone hypersensitivity.⁹ No CD63 up-regulation was observed with povidone in our patient (Fig 1).

The patient's type 3 reaction was characterized by fever, arthralgia, and purpuric rash. Amiodarone-induced vasculitis and type 3 reactions have been rarely reported, with approximately 10 cases cited in the literature.³

Many cutaneous adverse reactions of amiodarone are described, the most common being photodermatitis. Amiodarone may rarely cause life-threatening reactions, such as toxic epidermal necrolysis.⁴ Our patient's type 4 reaction is characterized by desquamating rash, erythroderma, lymphadenopathy, and transaminitis, which did not satisfy the criteria for a drug reaction with eosinophilia and systemic syndrome reaction. Our in vitro studies did not find lymphocyte proliferation, but it has been reported that

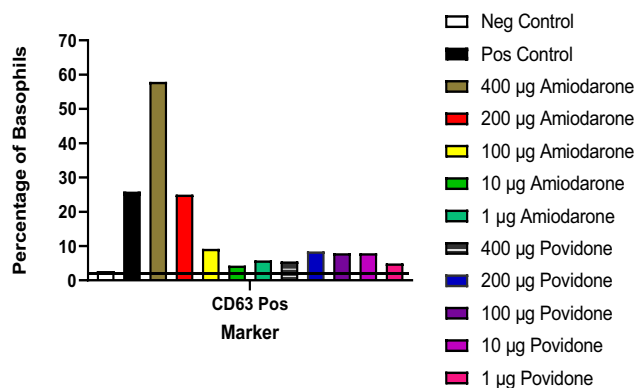


Figure 1. Basophil activation testing showing stimulation of CD63 at 400 and 200 µg of amiodarone with no response to the excipient povidone.

lymphocyte transformation tests have limited sensitivity in the diagnosis of delayed hypersensitivity reactions.¹⁰

This unique case demonstrates a mixed drug reaction to amiodarone and the potential utility of BAT for immediate hypersensitivity reactions in which skin testing is not possible or if skin testing is not well standardized. However, despite the positive BAT result to oral amiodarone in our patient and intravenous amiodarone as reported by another group,⁸ continued improvement of in vitro techniques to investigate immediate and delayed hypersensitivity reactions is needed.

Suran L. Fernando, PhD^{*,†,‡}

Jamma Li, MPhil^{*,†,‡}

Arunima Jain, MChD[§]

Christopher Weir, PhD^{*}

Therese Boyle, MBBCh, BAO, BA^{*}

^{*}Immunorheumatology Laboratory
New South Wales Health Pathology

Royal North Shore Hospital
Sydney, Australia

[†]Department of Clinical Immunology and Allergy
Royal North Shore Hospital
Sydney, Australia

[‡]University of Sydney
Sydney, Australia

[§]Department of Cardiology
Gosford Hospital
Gosford, Australia

suran.fernando@health.nsw.gov.au

References

- Colunga Biancatelli RM, Congedo V, Calvosa L, Ciacciarelli M, Polidoro A, Iuliano L. Adverse reactions of amiodarone. *J Geriatr Cardiol.* 2019;16(7):552–566.
- Okuyan H, Altin C, Arihan O. Anaphylaxis during intravenous administration of amiodarone [published correction appears in *Ann Card Anaesth.* 2013;16(4):282]. *Ann Card Anaesth.* 2013;16(3):229–230.
- Ndiaye M, Lebrun-Vignes B, Ortonne N, Fardet L. Amiodarone-induced immune complex cutaneous vasculitis. *Ann Dermatol Venereol.* 2017;144(12):788–792.
- Chen A, Sauer W, Nguyen DT. A dire reaction: rash after amiodarone administration. *Am J Med.* 2013;126(4):301–303.
- Li J, Best OG, Rose MA, Green SL, Fulton RB, Fernando SL. Integrating basophil activation tests into evaluation of perioperative anaphylaxis to neuromuscular blocking agents. *Br J Anaesth.* 2019;123(1):e135–e143.
- Porebski G, Gschwend-Zawodniak A, Pichler WJ. In vitro diagnosis of T cell-mediated drug allergy. *Clin Exp Allergy.* 2011;41(4):461–470.
- Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol.* 2010;105(4):259–273.
- Vilchez Sánchez F, Lluch Bernal M, González Muñoz M, Marques Mejías MA, Quirce S, Cabañas Moreno R. Usefulness of the basophil activation test in the diagnosis of hypersensitivity to amiodarone. *J Investig Allergol Clin Immunol.* 2019;29(5):378–379.
- Lakshmanadoss U, Lindsley J, Glick D, Twilley CH, Lewin 3rd JJ, Marine JE. Incidence of amiodarone hypersensitivity in patients with previous allergy to iodine or iodinated contrast agents. *Pharmacotherapy.* 2012;32(7):618–622.
- Cheung M, Seres T, Cleveland J, Kounis NG. Kounis syndrome, a coronary hypersensitivity disorder: a rare case of amiodarone-induced coronary vasospasm and simultaneous peripheral vasodilation intraoperatively. *Int J Cardiol.* 2016;218:267–268.

Systemic contact dermatitis to inhaled and intranasal corticosteroids



Systemic contact dermatitis (SCD) occurs when a sensitized individual develops a rash after systemic exposure to an allergen. The rash can occur at sites of previous dermatitis (or patch tests) or previously unaffected skin, such as in baboon syndrome.¹ Sensitization to corticosteroids is present in 0.5% to 5% of patients undergoing patch testing.² It is hypothesized that glyoxal and glutaraldehyde, metabolites of corticosteroids, act as haptens and bind to skin proteins, notably arginine, promoting sensitization.² Because SCD owing to inhaled or intranasal corticosteroid use is uncommon, we summarize the clinical characteristics of these patients through a systematic literature review, including a patient from our institution.

A 47-year-old woman with allergic rhinitis and asthma was evaluated at our institution for a pruritic maculopapular rash that developed within 24 hours of starting inhaled budesonide-formoterol. She was switched to inhaled fluticasone with resolution of the rash. She later underwent a toenail procedure with development of a rash to the adhesive tape site. She applied topical hydrocortisone, but the rash worsened. Patch testing using the

Thin-Layer Rapid-Use Epicutaneous test panel revealed sensitization to budesonide, hydrocortisone-17-butyrate, formaldehyde resin, and gold sodium thiosulfate.

We searched the PubMed database on December 20, 2019, using the following terms: “eczematous,” “contact dermatitis,” OR “skin reaction” AND either “inhaled corticosteroid,” “nasal corticosteroid,” “budesonide,” “beclomethasone,” “beclomethasone,” “mometasone,” “flunisolide,” “tixocortol pivalate,” OR “fluticasone.” No time or field restrictions were applied. Articles were filtered to include only English-language human studies. Original case reports, retrospective, or prospective studies describing patients with SCD to inhaled or intranasal corticosteroids were included. Studies describing isolated local (limited to the mouth, nose, or face) or immediate-type reactions were excluded. Clinical variables of interest were extracted. Our primary outcome was the clinical characteristics of patients. Secondary outcomes included clinical course, utility of patch testing, and knowledge of cross-reactivity using the Coopman classification² in identifying safe alternatives.

The PubMed search identified 308 records, of which 14 met the inclusion criteria: 13 case reports, 1 prospective study,³ and 1 cross-sectional study. Table 1 summarizes these studies. We added the abovementioned patient for a total of 19 patients, of which 89%

Disclosures: The authors have no conflicts of interests to report.

Funding: The authors have no funding sources to report.