

Hypersensitivity Reaction to Amiodarone in a Patient with a Previous Reaction to an Iodinated Radiocontrast Agent

Leanne Stafford

Amiodarone hydrochloride is a class AIII antiarrhythmic agent licensed in Australia for the management of severe tachyarrhythmias unresponsive to other therapy.¹ This includes atrial fibrillation in Australia, but not in the US.² Amiodarone is nevertheless becoming the drug of choice in the treatment of atrial fibrillation in many clinical situations,³ including treatment of postoperative atrial fibrillation, a complication that occurs in 10–65% of patients after cardiac surgery.⁴ This practice has been further supported by recent clinical guidelines.⁵ While amiodarone is effective in this setting, even short-term use confers a significant risk of potentially serious acute toxicities. These include cardiovascular effects (bradycardia, hypotension, circulatory collapse) and early-onset amiodarone-induced pulmonary toxicity,¹ which some have suggested has an immunologic mechanism.⁶ A hypersensitivity syndrome characterized by vasculitis, renal involvement, and thrombocytopenia has also rarely been described.¹

Amiodarone hydrochloride has a substantial iodine content, with each 200 mg tablet containing approximately 75 mg (and the injection containing 18.75 mg/mL) of organic iodine. At steady-state, metabolism of 300 mg of amiodarone yields 9 mg of iodine daily.¹ As a result of this high iodine content and the potential risk of cross-reactivity, the approved product information for amiodarone states that

OBJECTIVE: To describe a case of a hypersensitivity reaction to oral amiodarone in a patient with a previous reaction to an iodinated radiocontrast agent.

CASE SUMMARY: A 55-year-old man experienced facial urticaria after intraarterial injection of iohexol, an iodinated radiocontrast agent, during coronary angiography, which was successfully treated with intravenous hydrocortisone and promethazine. The procedure revealed significant triple vessel disease, and the patient subsequently underwent coronary artery bypass grafting in October 2006. Postoperatively, the patient experienced 2 episodes of fast atrial fibrillation, the first of which was treated successfully with intravenous amiodarone. The second episode resulted in the commencement of therapy with oral amiodarone 400 mg 3 times daily. Within one hour after the first dose, the patient experienced lip swelling and tingling, which was again treated with intravenous promethazine. Amiodarone was stopped; the patient remained in sinus rhythm and was discharged without further incident.

DISCUSSION: Amiodarone is a class III antiarrhythmic agent frequently used in the management of atrial fibrillation after cardiac surgery. The approved product information lists known hypersensitivity to iodine as a contraindication to its administration, but no other cases of amiodarone hypersensitivity in a patient with a previous reaction to an iodinated radiocontrast agent have been published. Conversely, it has been suggested that the drug may be safely used in such patients. The Naranjo probability scale supported a probable adverse reaction of hypersensitivity associated with amiodarone therapy in this patient.

CONCLUSIONS: Prescribers should exercise caution in the administration of amiodarone to patients with a true, documented history of hypersensitivity to an iodinated compound.

KEY WORDS: amiodarone, cross-reactivity, hypersensitivity, iodine, iohexol, radiocontrast.

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hypersensitivity to iodine is a contraindication to its administration. However, prescribers remain largely unaware of the iodine content of amiodarone, and the potential risk is rarely considered when selecting antiarrhythmic therapy.⁷

To highlight this risk, a case of a hypersensitivity reaction to oral amiodarone in a patient with a previous reaction to an iodinated radiocontrast agent is described.

Author information provided at the end of the text.

Case Report

A 55-year-old man was admitted to the hospital in August 2006 for elective angiography after a previous admission for unstable angina a month earlier. His medical history included ischemic heart disease, including uneventful percutaneous coronary angioplasty with stenting of his right coronary artery in March 2005; hypertension; hyperlipidemia; transient ischemic attacks; spasmodic torticollis; gastroesophageal reflux disease; anxiety; and amaurosis fugax of his right eye. Medications on admission were aspirin, clopidogrel, metoprolol, atorvastatin, nicorandil, and omeprazole. He had experienced angioedema with administration of irbesartan at an unspecified date and subsequently with ramipril in March 2005.

The angiographic procedure proceeded uneventfully until the patient reported an itchy face during injection of a radiocontrast agent containing iohexol 755 mg/mL (equivalent to iodine 350 mg/mL; Omnipaque 350) into his right coronary artery. Urticaria subsequently appeared on his face and neck, and he was treated with intravenous hydrocortisone 200 mg and promethazine 12.5 mg with good effect. The procedure was aborted, having revealed occlusion of the stent in his right coronary artery and significant stenosis of his circumflex and left anterior descending arteries. A total of 62 mL of Omnipaque 350 had been injected. The patient was subsequently scheduled for coronary artery bypass grafting of the 3 arteries on October 4, 2006, but was readmitted on September 30 with a diagnosis of troponin-positive unstable angina (troponin T 0.03 μ g/mL; normal <0.03) with runs of ventricular tachycardia. He was monitored leading up to his surgery, which was performed successfully on October 5.

Postoperatively on the day of surgery, the patient developed fast atrial fibrillation and was treated with an intravenous loading dose of amiodarone 300 mg in 100 mL of glucose 5% infused over 1 hour, then 600 mg in 250 mL of glucose 5% over 12 hours, which resulted in reversion to sinus rhythm. The remainder of his immediate postoperative course was unremarkable until October 8, when he experienced palpitations and an electrocardiogram demonstrated fast atrial fibrillation with a heart rate of 111–132 beats/min. Metoprolol was administered and the rhythm reverted spontaneously to sinus rhythm; oral amiodarone 400 mg 3 times daily was initiated as prophylaxis against further episodes. Therapy was started, before the patient had eaten, at 1130 hours that day. Within one hour of administration of the first dose, he experienced lip swelling and tingling, which resolved after treatment with a single dose of intravenous promethazine 12.5 mg. At this time, the patient was also prescribed aspirin, metoprolol, atorvastatin, omeprazole, acetaminophen, tramadol, and subcutaneous heparin. Amiodarone was stopped, as it was suspected of causing the reaction. The patient remained in

sinus rhythm and was discharged on October 11, with a recommendation for further investigation of his allergies.

Discussion

This is the first published case in the English literature of a patient with a documented allergy to an iodinated compound who subsequently developed a hypersensitivity reaction upon exposure to amiodarone.

Immediate hypersensitivity-like or anaphylactoid reactions are a well-recognized risk associated with the administration of iodinated radiocontrast agents, occurring in 1–2% of patients and comprising 20–30% of the reactions to radiocontrast agents.^{7,8} Such reactions often involve cutaneous manifestations, including urticaria, as experienced by this patient, although cardiovascular (hypotension, tachycardia), gastrointestinal (nausea and vomiting) and respiratory (dyspnea, laryngeal edema, bronchospasm) effects are also recognized.⁸

There remains some debate as to the cause of anaphylactoid reactions to iodinated radiocontrast agents. Although some researchers argue that they are due to an immunoglobulin E (IgE)-mediated mechanism, others favor either a non-specific histamine release associated with the hyperosmolarity of the solution or direct chemical toxicity, suggesting that an allergy to the iodine content of the radiocontrast agent is not the cause of the responses observed.^{7,8}

A number of factors are accepted as increasing an individual's risk of reactions to radiocontrast agents—most importantly, a history of allergy, atopy, or asthma and a previous reaction to radiocontrast agents, which is significant for one-third of patients with a previous reaction.^{7,8} While this patient had experienced uneventful exposure to a radiocontrast agent during his angioplasty 17 months prior to the events described, he had developed perioral angioedema with administration of irbesartan at a previous unspecified date and subsequently with ramipril. The onset of the effect was consistent with that usually observed with angiotensin-converting enzyme (ACE) inhibitor-induced angioedema,⁹ the patient having presented again to the emergency department with extensive swelling of the lips, cheeks, and neck within 2 weeks of initiation of ramipril and less than one week after upward titration of his dose to 10 mg daily. At this time, it was noted that the patient had experienced a similar reaction to irbesartan some years previously, but no further details were available. Angioedema associated with ACE inhibitors (and possibly angiotensin II receptor antagonists) is believed to be due to bradykinin accumulation rather than IgE-mediated histamine release,^{9,10} and although cross-reactivity between these agents has been recognized, it is not universal. This patient's reactions to both drugs therefore tend to suggest a "reactive" tendency. It must be noted that neither irbesartan nor ramipril contain iodine within their molecular structure.

The Naranjo probability scale suggested a probable adverse reaction of hypersensitivity associated with amiodarone therapy in this patient with a documented allergy to an iodinated radiocontrast agent.¹¹ This was supported by the strong temporal relationship with the first dose of oral amiodarone; the onset of the effect correlated with the time required for preliminary absorption from an oral dosage form, while allowing for amiodarone's slow, erratic oral absorption.¹ Furthermore, at the time of the reaction, the patient had been taking most of his concurrent drug therapy without incident for the previous 17 months. None of his newly started postoperative therapies (acetaminophen, tramadol, and heparin) had caused a reaction in the preceding 3 days and all drugs continued to be administered uneventfully until discharge. No other drugs or topical preparations had been administered or applied in the one and a half hours preceding amiodarone administration, and there had also been no subsequent administration of radiocontrast media or any other iodinated compound after his angiogram in August. A food reaction was considered highly improbable. Therefore, while it is difficult to rationalize the rapid resolution of the reaction after drug discontinuation and a single dose of promethazine given the long half-life of amiodarone (17–32 h after a single oral dose),² no other potential causes of the reaction were obvious. Promethazine is a long-acting member of its class, with a half-life of 7–15 hours and a duration of antihistaminic effect of up to 12 hours,^{2,12} which may have been sufficient to counteract the acute period of the hypersensitivity reaction.

A literature search of the PubMed (1950–March 2007), MEDLINE (1966–March 2007), CINAHL (1982–March 2007), Science Direct (1994–March 2007), EMBASE (1980–March 2007), and *International Pharmaceutical Abstracts* (1970–March 2007) databases using the search terms amiodarone, iodine, radiocontrast, allergy, hypersensitivity, anaphylaxis, angioedema, and cross-reactivity revealed 4 relevant papers. One of these detailed a case of anaphylaxis associated with administration of intravenous amiodarone¹³ and 2 reported angioedema with chronic oral administration.^{14,15} None of these patients had a documented history of a reaction to an iodinated compound. The fourth article, detailing the use of amiodarone in patients with previous documented allergies to iodine-containing compounds, is discussed below.⁷ A small number of cases of amiodarone hypersensitivity have also been reported to the manufacturer in postmarketing surveillance (personal communication, Richard Worrell BPharm, sanofi-aventis Medical Information Department, February 8, 2007).

A search of the Australian Adverse Drug Reactions Advisory Committee database revealed 3 case reports of allergic, hypersensitivity, anaphylactic, or anaphylactoid reactions to amiodarone (personal communication, Margaret Ward Curran MB ChB MPH, Adverse Drug Reactions Unit, Therapeutic Goods Administration, April 26, 2007).

Two of these reports (one the previously mentioned published case¹³) described anaphylactic reactions following intravenous amiodarone administration. Neither mentioned whether the patients involved had documented iodine allergies. The third report detailed eosinophilia, leukocytosis, photosensitivity, and pruritus in a 50-year-old woman taking oral amiodarone, verapamil, disopyramide, digoxin, and docusate sodium with danthron. Digoxin and docusate sodium with danthron were also suspected of possibly being causally related to the reaction. Although this woman's reaction differed from that experienced by our patient, it is interesting to note that she was also reported to be allergic to "X-ray contrast dyes," as well as to tomatoes, coffee, alcohol, sulfas, and amoxicillin. Despite a number of possible complicating factors, this unpublished case report was the only previous reference to a patient having potentially experienced reactions to both amiodarone and an iodine-containing compound.

Our patient's reaction to amiodarone may have represented a new allergy for him, and his previous reaction to the iodinated radiocontrast agent may have been coincidental. The amiodarone approved product information, however, states that "known hypersensitivity to iodine" is a contraindication to its administration,¹ a recommendation based solely on its high iodine content; thus, the possibility of cross-reactivity is worthy of consideration. Brouse and Phillips⁷ described 3 patients with previous documented allergies to iodine-containing compounds who received both intravenous and oral amiodarone without subsequent reactions. The source of iodine exposure in 2 of these patients was radiocontrast media, whereas one patient reported an allergy to shrimp and could not recall any previous reaction during administration of oral or intravenous radiocontrast agents or topical iodine-containing preparations. Another recent report supported the safety of amiodarone in patients with allergies to shellfish.¹⁶ This paper detailed uneventful amiodarone administration to such a patient and claimed that shellfish allergies are most likely due to tropomyosin, an allergen in shrimp and lobster, rather than their iodine content. Thus, the authors determined that "a shellfish allergy does not necessarily imply an iodine allergy."¹⁶ Brouse and Phillips⁷ also concluded that severe reactions to iodine-containing products are rare and often due to other substances in the formulation or other factors. However, there remains a "need for close monitoring of all patients with possible iodine-related reactions who are receiving amiodarone therapy."

One unexpected facet of our patient's presentation was his failure to react to intravenous amiodarone. It has been suggested that the complete bioavailability of the intravenous amiodarone formulation compared with its oral bioavailability of 22–86%¹ would be expected to increase the amount of iodine absorbed and thus increase the risk of reaction.⁷ However, this patient tolerated 900 mg of intra-

venous amiodarone administered over a period of 13 hours 3 days prior to experiencing the lip tingling and swelling within one hour of the administration of a single 400 mg oral dose. This led to the hypothesis that the reaction observed was in fact not related to amiodarone, but to one of the excipients in the tablet formulation (lactose, maize starch, povidone, magnesium stearate, colloidal anhydrous silica).¹ Each of these ingredients, however, was present as an excipient in at least one of the other tablets that the patient had been taking daily since his discharge from the hospital in March 2005, rendering them an unlikely cause. Alternatively, the intravenous dose may have sensitized the patient to amiodarone, resulting in the rapid response upon oral reexposure.

Finally, the involvement of the patient's face in this reaction resulted in the suggestion that this might be a case of iododerma, a skin reaction that occurs in response to the ingestion of iodides. It has also been induced by administration of amiodarone and iodinated radiocontrast agents.^{17,18} Iododerma, however, is characterized by a pustular facial rash with a delayed onset and longer clinical course inconsistent with this patient's observed symptoms, rendering this diagnosis unlikely in this case.

Conclusions

Although anaphylactoid reactions to iodinated radiocontrast agents may not be related solely to their iodine content, this report of a hypersensitivity reaction to oral amiodarone in a patient with a previous reaction to an iodinated radiocontrast agent raises the possibility of iodine being the common factor in these reactions. The literature suggests that cross-reactivity does not always occur, but a "known hypersensitivity to iodine" remains listed in the approved product information as a contraindication to amiodarone administration. Prescribers should therefore exercise caution in the administration of amiodarone to patients with an authentic documented history of hypersensitivity to iodine, including iodinated radiocontrast media. Alternative antiarrhythmic agents should be considered, and if none exist, appropriate resuscitation equipment should be available during the initial period of amiodarone administration.

Leanne Stafford BPharm(Hons) (Curtin) MPS MSHP, Lecturer, School of Pharmacy, Curtin University of Technology, Bentley, Western Australia, Australia; Clinical Pharmacist, Fremantle Hospital and Health Service, Fremantle, Western Australia

Reprints: Miss Stafford, School of Pharmacy, Curtin University of Technology, GPO Box U1987, Perth, WA 6845, Australia, fax 61 8 9266 2769, L.Stafford@curtin.edu.au

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Un Caso de Hipersensibilidad a Amiodarona en un Paciente con una Reacción Previa a un Agente Yodado de Radiocontraste

L Stafford

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EXTRACTO

OBJETIVO: Describir un caso de una reacción de hipersensibilidad a la amiodarona oral en un paciente con una reacción previa a un agente yodado de radiocontraste.

RESUMEN DEL CASO: Un hombre de 55 años de edad experimentó urticaria facial durante una angiografía coronaria, después de recibir una inyección intraarterial de iohexol, un agente yodado de radiocontraste. La urticaria fue tratada exitosamente con hidrocortisona y prometacina intravenosas. La angiografía reveló una enfermedad significativa en 3 vasos y el paciente fue sometido posteriormente a una cirugía de derivación de la arteria coronaria con injerto en octubre 2006. Después de la cirugía, el paciente sufrió 2 episodios de fibrilación atrial rápida, el primero de los cuales fue tratado exitosamente con amiodarona intravenosa. El segundo episodio resultó en el comienzo de la terapia con amiodarona oral; poco después, el paciente experimentó hinchazón y comezón de los labios, lo que fue tratado con prometacina intravenosa nuevamente. Se discontinuó la amiodarona, el paciente permaneció en ritmo sinusal y fue dado de alta sin ningún incidente adicional.

DISCUSIÓN: La amiodarona es un agente antiarrítmico Clase III que se usa frecuentemente en el manejo de fibrilación atrial después de una cirugía cardíaca. La Información aprobada sobre el producto incluye "una conocida hipersensibilidad al yodo" como una contraindicación para la administración de la amiodarona, pero en base a una búsqueda extensa de la literatura, no se ha publicado ningún caso anterior de hipersensibilidad a la amiodarona en un paciente con una reacción previa a un agente yodado de radiocontraste. Por el contrario, se ha sugerido que el fármaco puede ser usado con seguridad en tales pacientes. La escala de probabilidad de Naranjo confirmó una probable reacción adversa de hipersensibilidad asociada con la terapia de amiodarona en este paciente con una alergia documentada a un agente yodado de radiocontraste.

CONCLUSIONES: Los médicos prescribientes deben ejercer precaución en la administración de amiodarona a pacientes con un historial verdadero y documentado de hipersensibilidad a un compuesto yodado.

Traducido por Brenda R Morand

Reacción Alérgica a l'Amiodarone chez un Patient Ayant eu Auparavant une Réaction Alérgique aux Produits de Contraste Iodés

L. Stafford

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RÉSUMÉ

OBJECTIF: Décrire le cas d'une réaction allergique à l'amiodarone administrée par voie orale chez un patient ayant précédemment souffert d'une réaction allergique aux produits de contraste iodés.

RÉSUMÉ DU CAS: Un homme de 55 ans développa une urticaire faciale suite à l'administration d'iohexol, un produit de contraste iodé, dans le cadre d'une angiographie des artères coronaires. La réaction a répondu avec succès à l'administration intraveineuse d'hydrocortisone et de prométhazine. La procédure révéla une atteinte triple des coronaires qui fut subséquemment traité par un pontage coronarien en octobre 2006. En phase post-opératoire, le patient souffrit de fibrillation auriculaire à 2 reprises. Le premier épisode fut traité avec succès à l'amiodarone. Au second épisode, de l'amiodarone fut aussi instaurée, cependant, le patient développa une enflure des lèvres accompagnée de picotements qui furent traités avec succès avec de la prométhazine. L'amiodarone fut cessée et le patient quitta l'hôpital sans autre incident du rythme cardiaque.

DISCUSSION: L'amiodarone est un antiarythmisant de classe III fréquemment utilisée pour traiter les arythmies secondaires à la chirurgie cardiaque. La monographie indique hypersensibilité à l'iode au paragraphe contre-indications. Cependant, aucun cas d'allergie à l'amiodarone chez un patient connu comme allergique aux produits de contraste iodés, n'a pu être identifié dans la littérature médicale. Au contraire, il est même suggéré que l'administration d'amiodarone pourrait être sécuritaire chez de tels patients. L'échelle de Naranjo indique une relation probable entre la réaction allergique et l'administration d'amiodarone chez ce patient allergique aux produits de contraste iodés.

CONCLUSION: Les prescripteurs devraient être prudents lorsqu'ils administrent de l'amiodarone aux patients ayant déjà présentés une allergie aux produits de contraste iodés.

Traduit par Suzanne Laplante

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