

**CASE REPORT****Case Report of Sequential Rapid Valsartan Desensitization****Authors**

Scott T. Benken, PharmD, BCPS-AQ Cardiology, FCCM<sup>1</sup>, David J. Silva, PharmD<sup>1</sup>, Christen Vagts, MD<sup>2</sup>, Andrea A. Pappalardo, MD, FAAAAI<sup>2,3</sup>

**Affiliations**

<sup>1</sup>Department of Pharmacy Practice, University of Illinois at Chicago, 833 S Wood St, Chicago, IL, 60612, USA.

Electronic address: [dsilva8@uic.edu](mailto:dsilva8@uic.edu); [benken@uic.edu](mailto:benken@uic.edu)

<sup>2</sup>Department of Medicine, University of Illinois at Chicago, 1835 W Polk St, Chicago, IL, 60612, USA. Electronic address: [cvagts2@uic.edu](mailto:cvagts2@uic.edu)

<sup>3</sup>Department of Pediatrics, University of Illinois at Chicago, 1835 W Polk St, Chicago, IL, 60612, USA. Electronic address: [apappa2@uic.edu](mailto:apappa2@uic.edu)

**Correspondence**

Scott Benken, PharmD, BCPS-AQ Cardiology, FCCM University of Illinois at Chicago College of Pharmacy, 833 S Wood St, MC 886, Chicago, IL 60612. Phone: (312)355-4107. Fax: 312-996-0379.

Email: [benken@uic.edu](mailto:benken@uic.edu)

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**Abstract**

The literature surrounding oral antihypertensive desensitization procedures is limited. Desensitization is a therapeutic option for many medications but little information exists for anti-hypertensives, and no information exists for valsartan.

**Case description:**

A 55-year-old man developed hypersensitivity reactions to several antihypertensive medications, including valsartan. Multiple attempts were made trialing numerous anti-hypertensives. A 17-step rapid sequential oral desensitization procedure to valsartan was performed in this patient with successful tolerance and an absence of hypersensitivity reactions which led to adherence and chronic blood pressure control.

**Conclusion:**

To our knowledge this is the first report of valsartan desensitization. This successful intervention allowed for the patient to continue taking an essential antihypertensive medication necessary for optimal blood pressure control. The intention of this report is to help guide the management of complex patients who require desensitization to valsartan and to other antihypertensives in the future.

**Key words:** Desensitization; valsartan; allergy; hypersensitivity reaction; angiotensin receptor blocker.

## **Background:**

Drug desensitization requires slowly increasing the dose of a medication until an induced tolerance to a hypersensitivity reaction is achieved.<sup>1</sup> Desensitization is typically performed when therapeutic options are limited and IgE mediated hypersensitivity reactions are a concern.<sup>2</sup> A hypersensitivity reaction can occur when there is an amplified response of immune cells to an allergen or in this case, a medication.<sup>3</sup>

Antibiotics are well known to cause IgE mediated anaphylactic reactions including symptoms such as difficulty breathing, angioedema, hypotension, hives, and itching.<sup>4,5</sup>

The detection and standardized management of drug-induced allergic reactions to antihypertensive medications is limited.<sup>6</sup> This limitation can affect the available options to manage uncontrolled hypertension in a patient experiencing hypersensitivity reaction to these medications. We present a successful case of rapid oral desensitization to valsartan in a patient with a significant history of hypersensitivity reactions to commonly used antihypertensives.

## **Case description:**

The patient is a 55-year-old black man who has a past medical history of hypertension, hyperlipidemia, obesity, and asthma who was admitted after a lumbar surgery that was

complicated post-operatively by acute coronary syndrome. Within two days after the procedure he developed angioedema with facial swelling and shortness of breath which quickly responded to antihistamines and steroids. At this time all current medications, including aspirin 81 mg, atorvastatin, and a combination tablet amlodipine/valsartan, were continued.

Shortly after discharge the patient developed generalized pruritus and diffuse urticaria with intermittent chest pain which was relieved with diphenhydramine. The following month allergy-immunology was consulted and recommended discontinuation of aspirin, atorvastatin, and amlodipine/valsartan, although it was felt that aspirin use in the setting of acute coronary syndrome was the most likely causative agent.

One week later the patient was started on hydrochlorothiazide (HCTZ) for blood pressure control. Considering his condition might overlap with chronic idiopathic urticaria, daily cetirizine was also started. However, within two days he began to experience recurrence of urticaria with chest pain. He endorsed inconsistent use of cetirizine in providing mild, symptomatic relief after each episode. These symptoms did not cease and HCTZ was discontinued. Soon after, upon taking aspirin during an episode of shoulder pain, the patient presented to an outside hospital emergency department in anaphylactic shock with altered

mental status, dizziness, chest pain, urticaria, angioedema, and hypotension. He required intramuscular epinephrine, oral steroids and antihistamines resulting in resolution of anaphylaxis. A tryptase level was not drawn at this time as allergy service was not consulted; however, tryptase was checked the following month to evaluate for potential mast cell disorder, and levels were normal. Due to his history of presumed hypersensitivity reactions to various medications, the patient then underwent a series of drug challenges to test for drug-induced allergic reactions. The patient underwent skin testing to amlodipine at a concentration of 1 mg/mL (1:10) with a negative result. An oral drug challenge to amlodipine was then performed using a concentration of 1 mg/mL and starting at 0.1 mg. At the 1 mg dose he developed redness and itching of his upper left back along with mild chest discomfort. The challenge was stopped, and his symptoms resolved after taking diphenhydramine. The patient declined pursuing desensitization to amlodipine, so valsartan was approached next.

A valsartan skin test was performed beginning at a concentration of 4 mg/mL (1:10) but was terminated due to an inadequate histamine response. Notably, the negative histamine response could have been due to his inconsistent but continued use of cetirizine or due to supplementation with turmeric extract.<sup>6,7</sup>

Subsequent skin testing (5 mg/mL) and intradermal testing (0.5 mg/mL) to HCTZ were negative; however, the patient did not tolerate a HCTZ oral challenge performed using a concentration of 5 mg/mL liquid. At the 2.5 mg dose of this graded oral challenge, he experienced malaise and chest tightness which resolved shortly after taking fexofenadine. A HCTZ desensitization was then pursued but was terminated when the patient developed chest pain after the first dose and refused to continue the protocol.<sup>8</sup> He experienced relief with steroids and diphenhydramine, and a work-up for myocardial infarction was negative. Other antihypertensives initiated as an outpatient included metoprolol and doxazosin, but both produced a similar recurrence of urticaria and chest pain. Furosemide was tolerated, but the patient remained significantly hypertensive and required pursuit of other additional anti-hypertensive therapy.

With an increasingly limited number of antihypertensives available for this patient and without any existing protocols in the literature, a valsartan desensitization protocol was developed (Table 1). We decided to use an oral solution to allow for incremental stepwise dilutions. Increasing doses of valsartan were administered every fifteen minutes, with a total procedure duration of approximately four hours. The patient tolerated the desensitization without reactions nor intervention. The patient

is now tolerating valsartan daily and continues intermittent use of cetirizine.

**TABLE 1.** Valsartan oral suspension rapid desensitization

Step	Dosage of Valsartan (mg)	Cumulative Dose of Valsartan (mg)	Concentration of Valsartan (mg/mL)	Volume of Dose (mL)
1	0.0016 mg	0.0016 mg	0.004 mg/mL	0.4 mL
2	0.0032 mg	0.0048 mg	0.004 mg/mL	0.8 mL
3	0.0064 mg	0.0112 mg	0.004 mg/mL	1.6 mL
4	0.012 mg	0.0232 mg	0.04 mg/mL	0.3 mL
5	0.024mg	0.0472 mg	0.04 mg/mL	0.6 mL
6	0.052 mg	0.0992 mg	0.04 mg/mL	1.3 mL
7	0.104 mg	0.2032 mg	0.04 mg/mL	2.6 mL
8	0.2 mg	0.4032 mg	0.04 mg/mL	5 mL
9	0.4 mg	0.8032 mg	0.04 mg/mL	10 mL
10	0.8 mg	1.6032 mg	4 mg/mL	0.2 mL
11	1.6 mg	3.2032 mg	4 mg/mL	0.4 mL
12	3.2 mg	6.4032 mg	4 mg/mL	0.8 mL
13	6.4 mg	12.8032 mg	4 mg/mL	1.6 mL
14	13.2 mg	26.0032 mg	4 mg/mL	3.3 mL
15	26.4 mg	52.4032 mg	4 mg/mL	6.6 mL
16	52 mg	104.4032 mg	4 mg/mL	13 mL
17	104 mg	208.4032 mg	4 mg/mL	26 mL
<ol style="list-style-type: none"> <li>1. Make valsartan oral suspension 4 mg/mL</li> <li>2. Make a 1:100 dilution (0.04 mg/mL)                             <ol style="list-style-type: none"> <li>a. Mix 1 mL of 4 mg/mL oral suspension with 99 mL sterile water</li> </ol> </li> <li>3. Make a 1:10 dilution (0.004 mg/mL)</li> </ol>				

**Discussion:**

Though hypersensitivity reactions are relatively uncommon, they can lead to significant prescribing difficulties that severely limit medication choices.<sup>2</sup> According to the Joint National Committee – 8 guidelines for the management of hypertension, black patients should be initiated on HCTZ and/or calcium channel blocker as first line for blood pressure control.<sup>9,10</sup> Additionally, in patients with acute coronary syndrome, a compelling condition exists to utilize angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers.<sup>9,10</sup> Unfortunately, our patient had significant hypersensitivity reactions to first line agents HCTZ and amlodipine and failed challenge and desensitization to both agents. This intolerance was particularly problematic as the patient experienced significant uncontrolled blood pressure readings while without anti-hypertensive medications. This heightened the necessity of desensitization to another agent based on his compelling indications. Given the

patients' history of angioedema without a definitive cause, it was decided to avoid ACE-I and pursue desensitization to valsartan. Though desensitization has been described for some anti-hypertensive agents, a paucity of data still exists.<sup>8</sup> Our protocol was derived by extrapolating information from various oral antibiotic desensitization protocols.<sup>11</sup> This led to a graduated introduction of increasing concentrations to valsartan leading to tolerability, ongoing treatment, and successful blood pressure control.

**Conclusion:**

To our knowledge this is the first report of valsartan desensitization. This successful intervention allowed for the patient to continue an essential antihypertensive medication necessary for optimal blood pressure control. The intention of this report is to help guide the management of complex patients who require desensitization to valsartan and to other antihypertensives in the future.

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