Who ‘nose’, is it the angiotensin receptor neprilysin inhibitor?: a case series of persistent nasal pruritus in heart failure patients receiving sacubitril/valsartan

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Background
Sacubitril/valsartan is approved for the treatment of chronic heart failure with reduced left ventricular ejection fraction of ≤40% to decrease mortality and morbidity. Nasal pruritus is not a recognized adverse effect in the product information. In this case series, we encountered three patients who presented with nasal pruritus that improved after discontinuation of sacubitril/valsartan.

Case summary
Three patients aged 58–73 years-old presented with pruritus at the nasal septum post-initiation of sacubitril/valsartan. The pruritus did not subside despite the use of anti-histamines. Within 3–6 months, all individuals discontinued sacubitril/valsartan with complete resolution of their nasal pruritus.

Discussion
Many physicians may not aware of this unusual but reversible adverse effect of sacubitril/valsartan. Despite the positive prognostic value of sacubitril/valsartan, the constant nasal pruritus had impacted the quality of life of our patients, leading them to discontinue sacubitril/valsartan permanently.

Keywords
Sacubitril/valsartan • Entresto • ARNi • Nasal pruritus • Allergy • Case series

ESC Curriculum
6.2 Heart failure with reduced ejection fraction • 9.9 Cardiological consultations

Introduction
Sacubitril/valsartan is the first agent to be approved in a new class of medications called angiotensin receptor neprilysin inhibitor (ARNi). The medication is efficacious in reducing mortality and morbidity for the treatment of heart failure with reduced ejection fraction (HFrEF), defined as left ventricular ejection fraction (LVEF) ≤40%, when compared with standard therapy with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker. It is well known...
that ACE inhibition causes accumulation of bradykinin in the airways, which may contribute to the development of a dry cough. Bradykinin is metabolized by many different peptidases. Peptidase inhibitor therapies, such as ACEi and nephrilysin inhibitors, increase bradykinin levels (Figure 1). Accumulation of bradykinin may cause inflammation and angio-oedema. As such, sacubitril cannot be used with an ACEi, due to an increased risk of angio-oedema from bradykinin accumulation. When switching between ACEi and sacubitril/valsartan, the patient must undergo a 36-h washout period to lower the risk of angio-oedema.

There are some case reports of ACEi-induced nasal blockage, rhinitis, and postnasal drainage that improved after discontinuation of ACEi and substitution with angiotensin II receptor blockers. Little is known with sacubitril causing upper respiratory symptoms. In this anecdotal case series, we aimed to describe three individual cases of new-onset nasal pruritus, which temporally coincide with the initiation of sacubitril/valsartan. All three cases were being reviewed routinely in the multidisciplinary heart failure clinic at The Prince Charles Hospital, Brisbane, Australia.

### Case presentation

#### Case 1

A 69-year-old male with chemotherapy-induced cardiomyopathy, despite maximally tolerated medications (Table 1) and cardiac resynchronization therapy, presented with New York Heart Association (NYHA) of II and LVEF of 38% [index left ventricular end-diastolic volume (LVEDV) = 90 mL/m^2]. He was commenced on sacubitril/valsartan (49/51 mg) during a routine clinical review.

No known atopy, asthma or allergic rhinitis was documented at baseline. Other past medical histories include: type II diabetes mellitus, obstructive sleep apnoea, ex-smoker, previous pulmonary embolism, left tonsillar, and tongue cancer treated with chemoradiotherapy.

Known adverse drug reactions include diphenoxylate/atropine causing rash and trimethoprim/sulfamethoxazole causing dizziness. At a routine review 3 months after commencement of ARNi, the patient reported concern of nasal pruritus at the nasal septal area. The patient attributed the pruritus to the start of sacubitril/valsartan 49/51 mg twice daily, which occur within a week. Despite regular anti-histamine and a trial of decreasing the dose of sacubitril/valsartan to 24/26 mg twice daily, the nasal pruritus remained. Upon cessation of sacubitril/valsartan (and changing to ramipril), the nasal pruritus immediately resolved.

#### Case 2

A 73-year-old female with ischaemic cardiomyopathy (NYHA III; LVEF 18%; index LVEDV 143 mL/m^3) was commenced on low-dose sacubitril/valsartan (24/26 mg) after previously being on ramipril without known adverse reaction. The patient’s long-term anticoagulation for secondary prevention of deep venous thrombosis (DVT) was also changed from warfarin to apixaban at the same encounter (Table 1).

Patient’s past medical history includes coronary artery bypass, chronic obstructive pulmonary disease (smoker), type II diabetes mellitus, infra-renal abdominal aortic aneurysm, chronic back pain, and Hashimoto thyroiditis. Her adverse drug reactions were penicillin/cephalosporin causing hives, atenolol associated bronchospasm, and statins-related myalgia and visual disturbances.

The patient reported constant nasal pruritus within days after the commencement of sacubitril/valsartan and apixaban. Despite reassur-
Table 1  Patient’s medication lists and adverse drug reactions

| Case 1: |  
| Clinic 07 December 2018—medication list (commencement of sacubitril/valsartan) |  
| **Adverse drug reactions:** diphenoxylate/atropine—rash; trimethoprim/sulfamethoxazole—dizzy. |  
| Frusemide 40 mg | Take ONE tablet morning and midday. | New |  
| Potassium chloride sustained released 600 mg | Take ONE tablet morning and midday. | New |  
| Sacubitril-valsartan 49 mg/51 mg | Take ONE tablet morning and night. | New |  
| Bisoprolol 10 mg | Take HALF a tablet in the morning. | Unchanged |  
| Aspirin 100 mg | Take ONE tablet in the morning. | Unchanged |  
| Metformin 1000 mg | Take ONE tablet twice a day. | Unchanged |  
| Ascorbic acid | Take ONE daily when required. | Unchanged |  
| Calcium—magnesium—magnesium trisilicate | Chew ONE tablet daily as required. | Unchanged |  
| Ramipril 5 mg | Take ONE tablet morning. | Ceased—changed to sacubitril/valsartan |  
| Clinic 13 June 2019—Medication list |  
| Ramipril tabs 5 mg | Take ONE tablet morning. | New—to commence on 24 March 2019 |  
| Frusemide 40 mg | Take ONE tablet morning and midday. | Unchanged |  
| Potassium chlor sustained released 600 mg | Take ONE tablet twice a day. | Unchanged |  
| Bisoprolol 10 mg | Take HALF a tablet in the morning. | Unchanged |  
| Aspirin 100 mg | Take ONE tablet in the morning. | Unchanged |  
| Metformin 1000 mg | Take ONE tablet twice a day. | Unchanged |  
| Fexofenadine 180 mg | Take ONE tablet daily. | Unchanged |  
| Ascorbic acid | Take ONE daily when required. | Unchanged |  
| Calcium—magnesium—magnesium trisilicate | Chew ONE tablet daily as required. | Unchanged |  
| Sacubitril-valsartan 49/51 mg | Take ONE tablet twice a day. | Ceased—changed to Ramipril |  
| Clinic 21 March 2019—Medication list (cessation of sacubitril/valsartan) |  
| Ramipril tabs 5 mg | Take ONE tablet morning. | New—to commence on 24 March 2019 |  
| Frusemide 40 mg | Take ONE tablet morning and midday. | Unchanged |  
| Potassium chlor sustained released 600 mg | Take ONE tablet twice a day. | Unchanged |  
| Bisoprolol 10 mg | Take HALF a tablet in the morning. | Unchanged |  
| Aspirin 100 mg | Take ONE tablet in the morning. | Unchanged |  
| Metformin 1000 mg | Take ONE tablet twice a day. | Unchanged |  
| Fexofenadine 180 mg | Take ONE tablet daily. | Unchanged |  
| Ascorbic acid | Take ONE daily when required. | Unchanged |  
| Calcium—magnesium—magnesium trisilicate | Chew ONE tablet daily as required. | Unchanged |  
| Sacubitril-valsartan 49/51 mg | Take ONE tablet twice a day. | Ceased—changed to sacubitril/valsartan |  
| Case 2: |  
| Clinic 17 December 2018—Medication list (commencement of sacubitril/valsartan) |  
| **Adverse drug reactions:** amoxicillin—hives; atenolol—bronchospasm; atorvastatin—visual disturbances; HMG-CoA reductase inhibitors (statins)—myalgia; cephalosporins—hives. |  
| Apixaban 5 mg | Take ONE tablet twice a day. | New—to commence on 21 December 2018 |  
| Nebivolol 5 mg | Take HALF a tablet at night. | New—to commence on 19 December 2018 |  
| Sacubitril-valsartan 24 mg/26 mg | Take ONE tablet twice a day. | New—to commence on 24 December 2018 |  
| Frusemide (furosemide) 40 mg | Take ONE tablet in the morning. | Unchanged |  
| Potassium chloride sustained released 600 mg | Take TWO tablets in the morning. | Unchanged |  
| Empagliflozin/metformin 12.5 mg/1 g | Take ONE tablet twice a day. | Unchanged |  
| Insulin glargine 100 units/mL | Inject 38 units twice a day. | Unchanged |  
| Fenofibrate tabs 145 mg | Take ONE tablet at night. | Unchanged |  
| Thyrone (levothyroxine) 50 µg | Take ONE tablet in the morning. | Unchanged |  
| Fluticasone 100 microg/umeclidinium 62.5 µg/vilanterol 25 µg | Inhal ONE dose at night. | Unchanged |  
| Ipratropium 21 µg | Inhal TWO doses four times a day as required. | Unchanged |  
| Salbutamol 100 µg | Inhal TWO doses every four hours as required. | Unchanged |  
| Paracetamol 500 mg | Take TWO tablets four times a day as required. | Unchanged |  
| Magnesium 400 mg | Take TWO capsules daily when required. | Unchanged |  
| Dexamethasone 2 mg | Take ONE tablet daily when required. | Unchanged |  
| Diazepam 5 mg | Take ONE tablet at night when required. | Unchanged |  
| Warfarin | Variable dosage as directed by your INR blood test. Ceased on 18 December 2018—changed to apixaban |  
| Aspirin tabs 100 mg | Take ONE tablet in the morning. | Ceased—changed to apixaban |  
| Bisoprolol TABS 2.5 mg | Take HALF a tablet in the morning. | Ceased—changed to nebulol |  
| Ramipril tabs 2.5 mg | Take HALF a tablet twice a day. | Ceased on 21 December 2018—changed to sacubitril/valsartan |  
| Continued |  

### Table 1 Continued

#### Clinic 13 June 2019—Medication list

| Medicine                  | Dose/Concentration | Administration | Change  |
|---------------------------|--------------------|----------------|---------|
| Aspirin                   | 100 mg             | Take ONE tablet in the morning. | New     |
| Ramipril                  | 2.5 mg             | Take ONE tablet twice a day. | Unchanged|
| Nebivolol                 | 10 mg              | Take ONE tablet at night. | Unchanged|
| Frusemide (furosemide)    | 40 mg              | Take ONE tablet in the morning. | Unchanged|
| Potassium chloride sustained released 600 mg | | Take TWO tablets in the morning. | Unchanged|
| Empagliflozin/metformin   | 12.5 mg/1 g        | Take ONE tablet twice a day. | Unchanged|
| Insulin glargine 100 units/mL | | Inject 38 units twice a day. | Unchanged|
| Fenofibrate tabs 145 mg   |                    | Take ONE tablet at night. | Unchanged|
| Ezetimibe                 | 10 mg              | Take ONE tablet at night. | Unchanged|
| Thyroxine (levothyroxine) | 50 µg              | Take ONE tablet in the morning. | Unchanged|
| Fluticasone 100 µg/umeclidinium 62.5 µg/vilanterol 25 µg | | Inhalе ONE dose at night. | Unchanged|
| Ipratropium 21 µg         |                    | Inhalе TWO doses four times a day as required. | Unchanged|
| Salbutamol 100 µg         |                    | Inhalе TWO doses every four hours as required. | Unchanged|
| Paracetamol 500 mg        |                    | Take TWO tablets four times a day as required. | Unchanged|
| Magnesium 400 mg          |                    | Take TWO capsules daily when required. | Unchanged|
| Dextchlorpheniramine 2 mg |                    | Take ONE tablet daily when required. | Unchanged|
| Diazepam 5 mg             |                    | Take ONE tablet at night when required. | Unchanged|
| Colecalciferol (colecalciferol) 25 µg (1000 units) | | Take ONE tablet in the morning. | Unchanged|

Note: Patient stopped sacubitril/valsartan and apixaban during April 19.

#### Clinic 21 August 2019—Medication list

**Adverse drug reactions:** amoxycillin/clavulanic acid—hives; beta blockers—abdominal pain; calcium—nausea, pins, and needles; cephalexin—rash; diarrrhoea; clopidogrel—itching; fluticasone furoate—palpitations; fluvoxamine—diarrrhoea; methyl-
dopa—diarrrhoea; morphine—vomiting; ondansetron—leg swelling; pantoprazole/esomeprazole—cramps, hypomagnesaemia; quetiapine—rash; ramipril—hives, pins and needles; spironolactone—leg cramps; telmisartan—blurred vision.

| Medicine                  | Dose/Concentration | Administration | Change  |
|---------------------------|--------------------|----------------|---------|
| Sacubitril-valsartan 24 mg/26 mg | | Take ONE tablet in the morning. | Unchanged|
| Sacubitril-valsartan 49/51 mg | | Take ONE tablet at night. | Unchanged|
| Nebivolol                 | 10 mg              | Take ONE tablet at night. | Unchanged|
| Frusemide (furosemide)    | 40 mg              | Take HALF a tablet in the morning. | Unchanged|
| Magnesium                 |                    | Take ONE tablet in the morning. | Unchanged|
| Coenzyme Q10              |                    | Take ONE capsule in the morning. | Unchanged|
| Insulin aspartate mix30   |                    | Inject when blood sugar level is >12, administer FIVE units daily when required. Give with food. | Unchanged|
| Paracetamol 500 mg        |                    | Take TWO tablets four times a day as required. | Unchanged|
| Tramadol 50 mg            |                    | Take ONE capsule daily when required for migraines. | Unchanged|
| Rizatriptan 10 mg         |                    | Use ONE wafer on the tongue daily when required. | Unchanged|
| Ranitidine 150 mg         |                    | Take ONE tablet twice a day when required. | Unchanged|
| Salbutamol 100 µg         |                    | Inhalе TWO doses four times a day as required. | Unchanged|

Note: Patient was taking candesartan prior to sacubitril/valsartan; sacubitril/valsartan commenced in May 2019.

#### Clinic 28 January 2020—Medication list (cessation of sacubitril/valsartan)

| Medicine                  | Dose/Concentration | Administration | Change  |
|---------------------------|--------------------|----------------|---------|
| Candesartan 8 mg          |                    | Take ONE tablet in the twice a day. | New     |
| Nebivolol                 | 3 mg               | Take ONE tablet at night. | Unchanged|
| Frusemide (furosemide)    | 40 mg              | Take HALF a tablet in the morning as required. | Unchanged|
| Magnesium                 |                    | Take ONE tablet in the morning. | Unchanged|
| Coenzyme Q10              |                    | Take ONE capsule in the morning. | Unchanged|
| Insulin aspartate mix30   |                    | Inject when blood sugar level is >12, administer TEN units daily when required. Give with food. | Unchanged|
| Paracetamol 500 mg        |                    | Take TWO tablets four times a day as required. | Unchanged|
The patient reported constant nasal pruritus started three days after taking sacubitril/valsartan 24/26 mg twice daily, solely at the nasal septal area. Self-initiated daily use of anti-histamine medication was used to suppress the itch with no alleviation over 8 months. During this time, the dose was up-titrated to 49/51 mg twice daily, and then down-titrated to 24/26 mg twice daily (due to orthostatic hypotension), but the nasal itch remained constant. The sacubitril/valsartan 24/26 mg twice daily was ceased (as an initial trial) and was switched to candesartan, resulting in complete alleviation of the nasal pruritus.

| Medication                  | Dosage                                      | Status                        |
|-----------------------------|---------------------------------------------|-------------------------------|
| Tramadol 50 mg              | Take ONE capsule daily when required for migraines | Unchanged                     |
| Ranitidine 150 mg           | Take ONE tablet twice a day when required.   | Unchanged                     |
| Beclomethasone 100 µg       | Inhale ONE dose twice a day.                 | Unchanged                     |
| Salbutamol 100 µg           | Inhale TWO doses four times a day as required. | Unchanged                     |
| Loratadine 10 mg            | Take ONE tablet daily as required.           | Unchanged                     |
| Sacubitril-valsartan 24 mg  | Take ONE tablet twice a day.                 | Ceased—changed to candesartan |

**Discussion**

The clinical presentation of nasal pruritus post-initiation of sacubitril/valsartan is consistent between the three case reports. These cases were reported to the Australian pharmacovigilance authority (Therapeutic Goods Administration). All individuals described similar constant pruritus at the nasal septum; the same location for all three cases (Figure 2). Despite the use of anti-histamines, the pruritus did not subside. Interestingly, the severity of pruritus was not dose-dependent as a trial of down-titrating the sacubitril/valsartan dose did not alleviate the pruritus. As a result, all individuals discontinued sacubitril/valsartan within 3–8 months, with complete resolution of their nasal pruritus. Who ‘nose’, it may be the sacubitril/valsartan.

Several studies have highlighted a decline in the quality of life in patients suffering from symptoms of allergic rhinitis; it has been associated with increased risk of depression, behavioural and emotional disorders. The constant nasal pruritus experienced by our patients had been so severe that they had decided to discontinue sacubitril/valsartan. Upon cessation, there was a complete alleviation of nasal pruritus.
pruritus. All three patients in our series have declined to recom-
mence of sacubitril/valsartan despite experiencing symptomatic and
objective echocardiographic improvement of their underlying HFrEF.

Several chemical mediators, such as histamine, bradykinin, cysteinyl
leukotrienes, platelet-activating factor, prostaglandin D₂, and thrombo-
oxane A₂ are involved in the complex process of nasal allergic re-
sponse.8,9 Little is known about sacubitril causing nasal irritation. Most
literature discussed ACE inhibition causing bronchial mucosa irritation
were explained by bradykinin accumulation.8,10 Other mechanisms
potentiating this inflammatory reaction include histamine release from
mast cells due to bradykinin, substance P, leukotrienes, and prostaglan-
dins.10,11 Among patients with allergic airways, up-regulation of histo-
amine H₁ receptor in epithelial and vascular endothelial cells were
shown in immunohistochemical studies.8 Combination of both sacubi-
tril and valsartan may up-regulate the complex inter-play of chemical
mediators and receptors in a susceptible individual. However, the ad-
ministration of anti-histamine had not alleviated the symptom in our
patients. We attempted to perform a retrospective review to check
for shifts in blood counts (in particular eosinophils) and other inflam-
matory markers. As these tests were not routinely ordered in our
heart failure titration clinic, only one case (Case 3) had a baseline full
blood count recorded and there was no shift in the patient’s eosino-
phils during sacubitril/valsartan exposure. Of note, we have yet to
evaluate the effect of intra-nasal corticosteroids among these patients.

Interestingly, all the described cases in this series did not report sig-
ificant nasal congestion and rhinorrhea. We hypothesize that based
on this observational divergence as compared to allergic rhinitis, the
mediator(s) in ARNi-mediated nasal pruritus may not involve similar
extend of mast cells degranulation and histamine releases as observed
in seasonal and perennial allergic rhinitis. The symptoms of nasal prur-
itus may potentially be mediated by increased local bradykinin along
the nasal septum, rather than a true hypersensitivity response as in al-
lergic rhinitis (Figure 1). Nevertheless, unless immunohistochemical
analyses were performed to determine the expression and distribution
of these receptors in susceptible individual, we were unable to con-
clude which chemical mediators are driving the nasal pruritus.

Conclusion

Based on the known pharmacological effect of sacubitril on Brady-
kinin, the described cases of persistent but reversible nasal prur-
itus coinciding with the commencement of ARNi raises the
possibility of this less-known adverse drug reaction. Although the
effect of nasal symptoms is far less prognostically significant com-
pared to the adverse outcomes associated with HFrEF, the con-
stant nasal pruritus and the associated impact on the quality of
life and mood disturbance may prompt patient’s desire to discon-
tinue ARNi permanently.

Lead author biography

Jaclyn Gan is a clinical pharmacist who has been practicing in hospital
setting for the last 20 years, after completing her Bachelor of
Pharmacy at the University of Queensland in 2001. In 2007, she
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ral hospital in Brisbane, Australia, specializing in cardiology. Areas
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macy network.

Supplementary material

Supplementary material is available at European Heart Journal - Case
Reports online.

Slide sets: A fully edited slide set detailing this case and suitable for
local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission
and publication of this case report including images and associated
text has been obtained from the patient in line with COPE guidance.

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