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Clinical report

Successful antihypertensive treatment using sacubitril/valsartan alone in a patient with obstructive sleep apnoea syndrome

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ABSTRACT

Obstructive sleep apnoea syndrome (O-SAS) induces excessive activity of the sympathetic nervous system, resulting in secondary hypertension. Although continuous positive airway pressure (CPAP) is the first-line therapy for O-SAS, poor adherence to CPAP induces uncontrollable resistant hypertension. We present a case of O-SAS-related hypertension successfully treated with sacubitril/valsartan alone. Polysomnography before treatment showed a markedly increased apnoea-hypopnoea index (44.8/hour). While receiving treatment with CPAP and azilsartan, his in-office blood pressure remained within the acceptable range (120–130/80–85 mmHg). However, his blood pressure increased again after quitting CPAP. Subsequently, we switched to sacubitril/valsartan alone and succeeded in improving his blood pressure from 145/95 to 120/80 mmHg. Furthermore, sacubitril/valsartan improved sleep quality in terms of blood pressure (from non-dipper type to dipper type) and apnoea-hypopnoea index (38.3/hour). This case indicates that sacubitril/valsartan has great potential for antihypertensive effects in patients with severe O-SAS, even without CPAP.

Tratamiento antihipertensivo exitoso usando solo sacubitril/valsartán en paciente con síndrome de apnea obstructiva del sueño

Palabras clave:
síndrome de apnea obstructiva del sueño
hipertensión
sacubitril/valsartán

RESUMEN

El síndrome de apnea obstructiva del sueño (SAOS) induce actividad excesiva del sistema nervioso simpático, ocasionando hipertensión secundaria. Aunque la presión positiva continua en vía respiratoria (CPAP) es el tratamiento inicial para SAOS, mala adherencia a CPAP provoca hipertensión resistente incontrolable. Presentamos un caso de hipertensión relacionada con SAOS tratada exitosamente solo con sacubitril/valsartán. La polisomnografía pre-tratamiento mostró un índice de apnea-hipopnea notablemente aumentado (44,8/hora). Tratando con CPAP y azilsartán, su presión arterial en consultorio permaneció en rango aceptable (120-130/80-85 mmHg). Pero, su presión arterial volvió a aumentar tras dejar la CPAP. Posteriormente, cambiamos a solo sacubitril/valsartán, consiguiendo mejorar su presión arterial (de 145/95 a 120/80 mmHg). Además, sacubitril/valsartán mejoró la calidad de sueño durante el sueño en términos de presión arterial (tipo no dipper a tipo dipper) y del índice de apnea-hipopnea (38,3/hora). Este caso demuestra que sacubitril/valsartán tiene un gran potencial de efectos antihipertensivos en pacientes con SAOS grave, incluso sin CPAP.

Introduction

Obstructive sleep apnoea syndrome (O-SAS) has a causal relationship to cardiovascular disease.[1] Although continuous positive airway pressure (CPAP) treatment is the gold standard treatment for moderate-to-severe O-SAS,[1,2] adherence to CPAP is often suboptimal and can induce uncontrolled hypertension. Moreover, current

Abbreviations: AHI, apnoea–hypopnoea index; BP, blood pressure; CPAP, continuous positive airway pressure; O-SAS, obstructive sleep apnoea syndrome.

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Table 1
Laboratory examination on first visit.

	Value	unit
White blood cell	6100	/μL
Red blood cell	539	$\times 10^4$/μL
Haemoglobin	15.9	g/dL
Haematocrit	46.5	%
Platelet	27.5	$\times 10^4$/μL
Aspartate aminotransferase	31	IU/L
Alanine aminotransferase	77	IU/L
Serum creatinine	0.88	mg/dL
Estimated Glomerular Filtration Rate	79	mL/min/1.73 m^2
Serum sodium	139	mEq/L
Serum potassium	4.3	mEq/L
Serum chloride	102	mEq/L
Cortisol	23.0	μg/dL
Active renin concentration (CLEIA)	10.4	pg/mL
Aldosterone (RIA)	258.0	pg/mL
Noradrenaline	0.02	ng/mL
Adrenaline	0.42	ng/mL
Dopamine	<0.01	ng/mL

CLEIA, chemiluminescence enzyme immunoassay: RIA, radioimmunoassay.

hypertension guidelines do not indicate antihypertensive drugs for treatment of hypertensive patients with O-SAS.[2]

Sacubitril/valsartan inhibits the activity of neprilysin and increases the blood levels of natriuretic peptides.[3] Natriuretic peptides have several systemic protective effects, such as natriuresis, inhibiting salt sensitivity, and decreasing sympathetic nervous outflow, which are potential factors influencing the pathophysiology of O-SAS with hypertension.[3] With this context, sacubitril/valsartan could be a strong option for correcting O-SAS with hypertension. However, no randomized trials or case reports have shown that it improves the severity of hypertension or the apnoea–hypopnoea index (AHI) in O-SAS patients.

We describe the case of a patient with O-SAS-related hypertension who could not continue CPAP. This case could contribute to selecting a medication for patients with O-SAS and future clinical practice.

Case introduction

A 38-year-old Japanese man was referred to our clinic for hypertension. He reported heavy alcohol consumption with an enlarged abdominal circumference (106 cm) and high body mass index (32.9 kg/m^2). His blood pressure (BP) was 160/104 mmHg. Laboratory endocrine examination revealed mildly elevated plasma aldosterone with normal active renin concentration and renin-to-aldosterone ratio (Table 1).

Administration of amlodipine 5 mg and switching to azilsartan 20 mg once daily did not lower his BP (145–160/90–105 mmHg; Fig. 1). He did not feel daytime hypersomnolence (Epworth Sleepiness Scale; 8), but his family members often noticed his loud snoring and apnoea during sleep. Polysomnography revealed an AHI of 44.8 events per hour, an apnoea index of 35.4 events per hour, a minimum sleep oxygen saturation level of 78 %, and a maximum apnoea/hypopnoea duration of 154 seconds. He was diagnosed with O-SAS-related hypertension and was administered CPAP with an average of 9.6 cm H_2O. Although he used CPAP only for 2 hours and 58 minutes on average for approximately 3 months, the AHI was 4.8/hour, and his BP remained within the normal range (120–130/75–85 mmHg, Fig. 1).

Due to his discomfort with wearing a CPAP mask during sleep, we made efforts to improve the situation by adjusting the positive pressure settings, changing the mask design, and providing educational intervention. However, the patient eventually opted to discontinue CPAP. Subsequently, his BP increased (150–160/85–95 mmHg); therefore, he was started on sacubitril/valsartan 200 mg once daily. His BP gradually decreased (120–130/80-90 mmHg; Fig. 1). Ambulatory blood pressure monitoring revealed that his BP improved during sleep from the non-dipper type (2 %) to the dipper type (14 %) after treatment with sacubitril/valsartan (Fig. 2 a, b). Furthermore, AHI and apnoea index on polysomnography also improved to 38.3/hour and 18.7/hour, respectively (Fig. 2c).

Ten months after starting sacubitril/valsartan, his BMI remains still high (30.7 kg/m^2), but he visits our clinic once a month and is treated with sacubitril/valsartan alone; his BP is within the acceptable range (120–130/80–90 mmHg, Fig. 1).

Discussion

O-SAS is a prevalent yet underdiagnosed chronic disorder. It is estimated that 5-10 % of hypertensive patients.[1,2] Although our patient had never experienced hypersomnolence, he was worried about his apnoea and snoring during his sleep. Physicians should perform a positive physical examination and polysomnography when physical characteristics and complications suggestive of O-SAS are found.[2]

Although CPAP is the first-line treatment for O-SAS, less than half of the patients achieve effective adherence to CPAP.[1,2,4] As in our case, CPAP is frequently discontinued if the treatment does not improve their quality of life or if they do not feel somnolence even though CPAP was very effective in decreasing the office blood pressure.

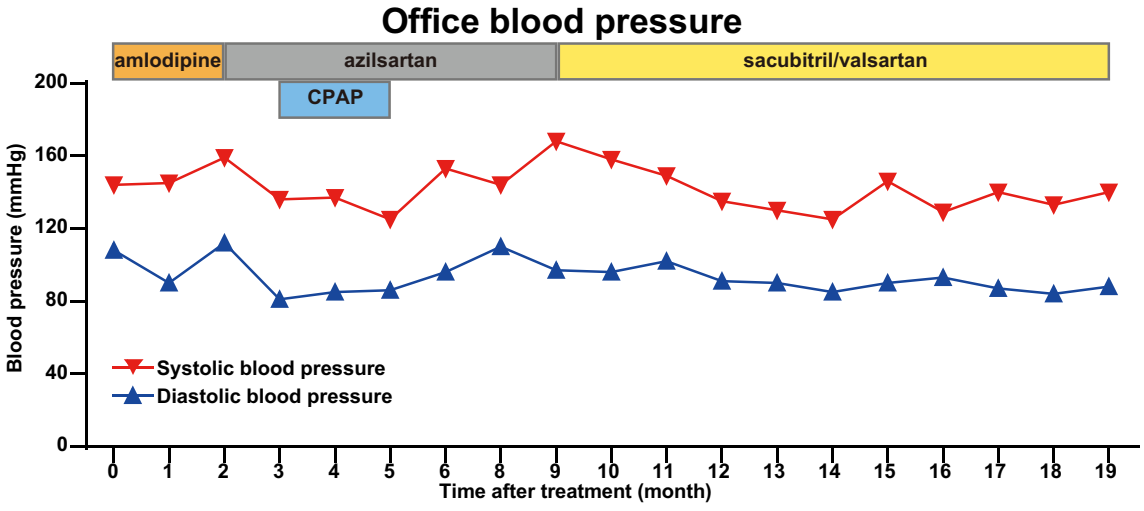

Fig. 1. In-office blood pressure at the first visit Daily doses of amlodipine, azilsartan, and sacubitril/valsartan were 5 mg, 20 mg, and 200 mg, respectively. CPAP, continuous positive airway pressure.

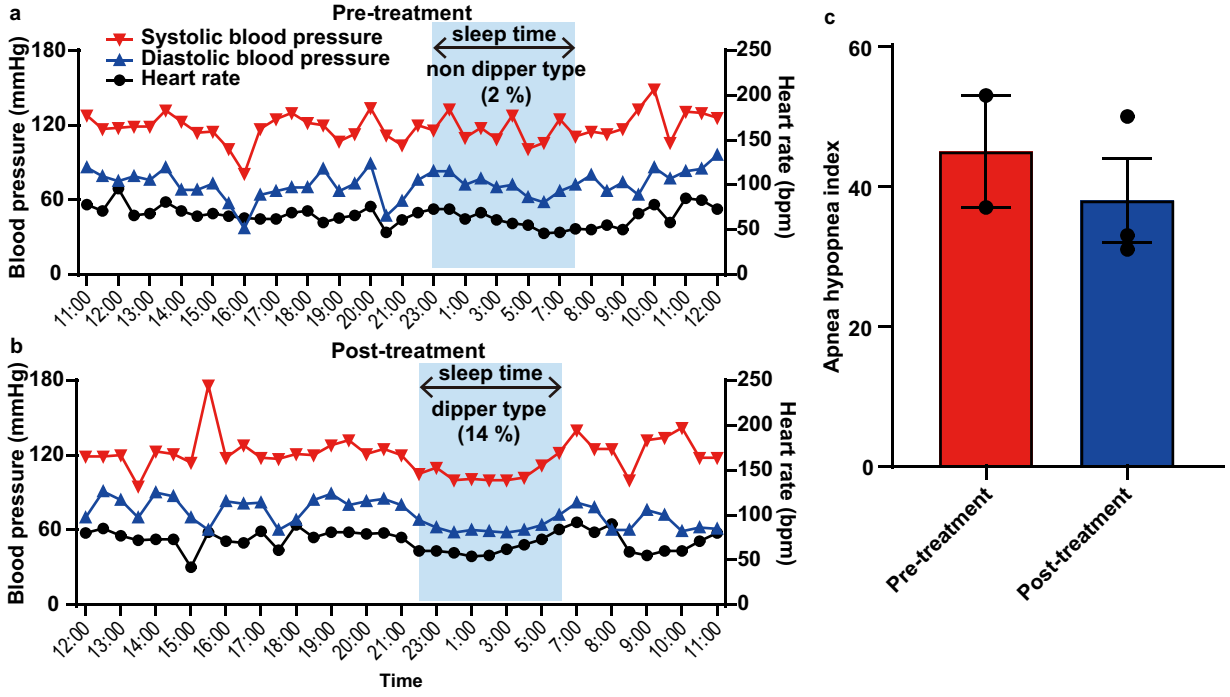

Fig. 2. Ambulatory blood pressure monitoring and apnoea-hypopnoea index Ambulatory blood pressure monitoring **a** before and **b** after sacubitril/valsartan treatment. Sleep duration is shown in blue. **c** Apnoea-hypopnoea index before and after treatment with sacubitril/valsartan. Data are expressed as the mean ± SEM.

Therefore, novel therapeutic targets that might complement CPAP in patients with O-SAS are worth investigating.

The excessive activity of the sympathetic nervous system and oedematous pharynx has been strongly implicated as mechanisms contributing to worsening O-SAS-induced hypertension.[1,2] Treatment options for managing sleep apnoea focus on addressing these mechanisms, such as diuretics, β-blockers, or renal sympathetic denervation, and have the potentials to decrease AHI more effectively in O-SAS patients.[5–7] However, these treatments are not yet regularly prescribed in clinical practice.

Sacubitril/valsartan can increase natriuretic peptides in the blood that can promote natriuresis and reduce sympathetic nerve outflow.[3] A previous study showed that sacubitril/valsartan without CPAP could significantly decrease AHI in patients with chronic heart failure.[8] This pleiotropic effect could have immense potential to decrease BP in patients with O-SAS. Our patient's hypertension was exacerbated by his continued consumption of alcohol and salty snacks at night. Since a calcium channel blocker or an angiotensin II receptor blocker failed to lower his BP, the natriuresis action of sacubitril/valsartan might counteract the increased salt consumption. Furthermore, sacubitril/valsartan might have ameliorated the overstimulation of the sympathetic nervous system caused by O-SAS.

In previous studies, obesity and alcohol consumption have been strongly associated with exacerbation of O-SAS.[9,10] Considering the specific characteristics of our case involving a young male patient, it is imperative to emphasize the need for weight reduction, reduction in alcohol intake, and decreased salt consumption. Considering his long future implications, we need to recognize the importance of maintaining regular guidance and to conduct a repeat polysomnography and actively encourage the reintroduction of CPAP, if deemed necessary.

Conclusion

Our case showed, for the first time, that sacubitril/valsartan may be a potential therapeutic option for O-SAS-induced hypertension compared to other oral medications. It could be considered as an adjunctive option to CPAP in a practical sense. In the future, more definitive clinical trials are needed to confirm this concept.

Ethical approval

No approval was required.

Informed consent

The patient provided written informed consent for publication of this manuscript.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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