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Case Report

Sinus bradycardia induced by thalidomide in rheumatic disease: two case reports

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Abstract: Thalidomide-induced sinus bradycardia is common in multiple myeloma (MM), but is less in rheumatic disease. Two cases of sinus bradycardia caused by thalidomide therapy for rheumatic disease are reported here. Case 1 was a patient with Behcet's disease, whose heart rate (HR) dropped from 81-96 bpm to 43-50 bpm after thalidomide treatment was increased to 150 mg daily. His HR returned to normal 1 week after discontinuation of thalidomide. Case 2 was a patient with hypersensitivity angiitis, whose HR was around 81-87 bpm before the addition of thalidomide. Her HR dropped to 42 bpm after thalidomide treatment was increased to 100 mg daily, but returned to normal 3 days after its discontinuation. Though thalidomide-induced sinus bradycardia is rare, thalidomide should be used with caution in patients with rheumatic diseases even in small dosage.

Keywords: Thalidomide, sinus bradycardia, Behcet's disease, hypersensitivity angiitis

Introduction

There have been a number of case reports about sinus bradycardia induced by thalidomide in MM [1], amyotrophic lateral sclerosis (ALS) [2], POEMS [3], and others, but this side effect is rare in rheumatic disease. The reason for this may be the small dosages used in rheumatic disease. Here, we report two cases in which sinus bradycardia was induced by thalidomide in rheumatic disease.

Case 1

A 29-year-old man with Behcet's disease who repeatedly suffered from oral ulcers and a rash for seven years was admitted to the hospital on September 17th, 2015. His first therapy regimen included the daily administration of 10 mg prednisone and 100 mg cyclosporine, and the weekly administration of 10 mg methotrexate. The above symptoms began to improve, but relapsed frequently. His therapy regimen was then changed with the addition of 50 mg daily thalidomide, 12.5 mg weekly methotrexate, and 100 mg monthly infliximab. During this period, the patient's HR was between 81 to 96 bpm. He did not take any drugs or have any concomitant diseases influencing HR. Due to the amelioration of the oral ulcers and the rash, the thalidomide was gradually increased to 150 mg daily, and the methotrexate was reduced to 7.5 mg weekly. The new regimen caused the continued improvement of both the ulcer and rash, however, he began to suffer from amaurosis and dizziness 2 weeks after the thalidomide dose increased. His HR was recorded as 43 to 50 bpm and the electrocardiogram (ECG) showed sinus bradycardia. Amaurosis and dizziness were not relieved until the thalidomide was completely withdrawn. His HR gradually returned to normal (78 to 86 bpm) one week after the discontinuation of thalidomide. At the follow up after discharge, his HR fluctuated between 76 and 85 bpm, and he had no future episodes of amaurosis or dizziness.

Case 2

A 39-year-old woman with hypersensitivity angiitis who repeatedly suffered from a rash with ulcers on her legs for 4 years was admitted to the hospital on January 4th, 2015. She had been treated with prednisone, cyclophosphamide, and mycophenolate mofetil, but the treatment effect was poor. Therefore, 25 to 50 mg of

Table 1. The similar cases about sinus bradycadia induced by thalidomide

Case	Diagnosis	Complication	Dosage of thalidomide
1	ALS [2]	Sinus bradycadia	Initiated at 100 mg/d ,and increased by 50 mg per week until reaching 400 mg
2	POEMS [4]	Sinus bradycadia	200 mg/d
3	RARS [9]	Sinus bradycadia	Initiated at 100 mg/d,and increased to 400 mg/d gradually
4	MM [1]	Sinus bradycadia	100 mg/d with beta-blocker

daily thalidomide was added to the therapy regimen. During this time, her HR was normal (81 to 87 bpm) and she did not take any drugs or have any concomitant diseases that influenced her HR. Her rash was not controlled until the dose was increased to 100 mg daily. She subsequently suffered from chest discomfort 2 weeks after the initiation of the increased dose of thalidomide. Her HR dropped to 42 bpm and an ECG showed sinus bradycardia. In consideration of the thalidomide-induced sinus bradycardia, thalidomide was discontinued, which caused the patient's chest discomfort to disappear and her HR to return to normal (76 to 82 bpm) 3 days later. During her follow up examination, it was clear that she no longer suffered from sinus bradycardia.

Discussion

Thalidomide was used as a sedative and was produced by a German medicine manufacturer called Grunenthal GmbH in 1957, but was withdrawn from the market because of its teratogenic effects [4]. Other pharmacological uses for thalidomide were found later, however, such as its antiangiogenic effect [5], inhibition of the chemotactic response of leukocytes in inflammation sites [6], selective inhibition of TNF-α expression, stimulation of natural killer cells, and enhanced production of IL-2 [7]. Recently, even more roles have been discovered, including the way in which thalidomide binds to the protein cereblon which can form an E3 ubiquitin ligase complex. This drug-protein combination can interfere with the activity of the E3 ubiquitin ligase complex that underpins the cytotoxic and immune-modulating effects of IMiDs [8]. Thalidomide was first applied to treat leprosy tubercles and multiple myeloma, then was used in Crohn's disease, systemic-onset juvenile idiopathic arthritis, systemic lupus erythematosus, and Behcet's disease [8], among others. With its clinical application, however, some side effects have been identified, such as neurotoxicity, gastrointestinal reactions, sleepiness, and cardiotoxicity, which includes sinus bradycardia [9], tachyarrhythmia [10], myocardial infarction, and third degree atrioventricular block [11]. Sinus bradycardia has been found in the treatment of multiple myeloma (MM) [1], refractory anemia with ringed sideroblasts (RARS) [9], ALS [2], POEMS [3], and other non-rheumatic disease with thalidomide (**Table 1**). The risk of sinus bradycardia resulting from thalidomide treatment is high in non-rheumatic diseases, especially multiple myeloma, in which the incidence of mild sinus bradycardia is about 25-50%, while severe sinus bradycardia accounts for 1%-3% [12]. The mechanism is still unclear. Chinghsueh Tsung [13] and Emch [14] have shown that the expression of TNF-α could inhibit the vagus nerve, which supplies visceral parasympathetic fibers to the heart. Nevertheless, the expression and activity of TNF-α can be inhibited by thalidomide. As a result, the inhibition of the vagus nerve is relieved, leading to sinus bradycardia. Some of these patients return to normal after discontinuation of thalidomide treatment, but some have to be implanted with a permanent pacemaker. Nevertheless, there are no such reports in patients with rheumatic disease. The clinical therapeutic dose of thalidomide for rheumatic disease is generally 25 to 200 mg daily. However, the usual dose of thalidomide in other diseases ranges from 100 mg to 400 mg daily, and the dose could reach 1200 mg daily in the treatment of some cancers [15]. We suggest that the reason that sinus bradycardia is rarely induced by thalidomide in patients with rheumatic diseases may be related to its small dosage.

Sinus bradycardia occurred in our patients when the dose of thalidomide was increased to 150 mg daily in Case 1 and 100 mg daily in Case 2. Both patients fully recovered after the discontinuation of thalidomide. Neither had a history of any diseases that influenced their HR, nor were they taking heart rate suppression drugs at the time, suggesting that thalido-

mide can also cause sinus bradycardia in the treatment of rheumatic disease, even with a smaller dosage. In addition, Yamaguchi [1] found that the combination of thalidomide and beta blockers can increase the risk of sinus bradycardia.

Since thalidomide is frequently used in rheumatic disease, clinicians should be aware of the possibility of drug-induced sinus bradycardia, especially when combined with beta blockers.

Disclosure of conflict of interest

None.

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