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Case Report

Hiccup Secondary to Amantadine in Traumatic Brain Injury: A Case Report

Wu YY[1], Wu YT[1,2], Chen LC[1,2] and Lin CY[2,3]*

[1]Department of Physical Medicine and Rehabilitation, Tri-Service General Hospital, National Defense Medical Center, Taiwan

[2]School of Medicine, National Defense Medical Center, Taiwan

[3]Department of Physical Medicine and Rehabilitation, Kaohsiung Armed Forces General Hospital, Taiwan

***Corresponding author:** Lin Ching-Yueh, Department of Physical Medicine and Rehabilitation, Kaohsiung Armed Forces General Hospital, Lingya, Kaohsiung City, Taiwan

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Abstract

Amantadine was reported to be a choice of treatment for conscious arousal in TBI patients by affecting the dopaminergic pathway. We report a case suffered from conscious disturbance after Traumatic Brain Injury (TBI), and developed persistent hiccups after initiating amantadine treatment for conscious arousal. Amantadine had only been reported to treat hiccups rather than a causal role. To our knowledge, this is the first case report that persistent hiccups develop secondary to amantadine in a TBI patient.

Keywords: Amantadine; Traumatic brain injury; Hiccups

Case Presentation

A 28-year-old young boy, who was healthy without any systemic disease before, was admitted to our Physical Medicine & Rehabilitation (PM&R) ward for further inpatient rehabilitation and Hyper Baric Oxygen Therapy (HBOT) due to prolonged minimally conscious status (Rancho Los Amigos Scale: IV- Confused/Agitated: Maximal Assistance~V-Confused, Inappropriate Non-Agitated: Maximal Assistance) after Traumatic Brain Injury (TBI) 4 months ago. On admission, physical examination showed decreased muscle strength (3/5 in left limbs, 4/5 in right limbs) and increased muscle tone in four limbs (Modified Ashworth Scale (MAS): 2 in upper limbs, 1+ in lower limbs, esp. in knee). His weight was 88kg. Both functional status and the Activities of Daily Living (ADL) were maximally dependent, even rolling on the bed. He received scheduled inpatient rehabilitation including physical therapy such as PROM, stretching, and balance training. HBO therapy was also ongoing during the hospitalization. To additionally improve conscious arousal, we prescribed amantadine 100mg once daily, which had been reported to be effective in this field [1,2].

After amantadine therapy, the patient began to utter some words and could obey simple commands intermittently. However, hiccups at a rate of 60/min (1/sec) began 2 days after the treatment of amantadine, and lasted for more than 48 hours. We tried to use metoclopramide, mosapride and simethicone to eliminate the patient's symptoms but in vain. We discontinued amantadine, then the hiccups stopped 24 hours later. Because of the significance in conscious improvement after using amantadine and uncertain association between hiccups and amantadine, we re-used amantadine 100mg once daily 7 days later. The patient developed hiccups 2 days later again. Due to persistent hiccups for more than 48 hours despite metoclopramide treatment, we tapered the dose to one dose of 100mg amantadine every other day and hiccups stopped immediately. Seven days later, we tried to increase the dose of amantadine to 150mg every other day, but hiccups developed again. After hiccups lasted for more than 48 hours and still refractory to any pharmacologic treatment, we tapered the dose down to 100mg every other day again, and hiccups never developed. During the hiccups intervals, the patient's life quality was severely affected including poor oral intake, sleep disturbance, and emotional irritability.

Discussion/Conclusion

Hiccup is defined as an involuntary, spasmodic contraction of diaphragm which was followed by sudden closure of the glottis [3,4]. It is thought to be mediated through the hiccup reflex arc, including afferent route (vagus nerve, phrenic nerve, sympathetic chain), efferent route (phrenic nerve, nerves to the glottis and the intercostal muscles), and the central mediator center [5]. Hiccups are usually brief and benign. However, persistent hiccups, lasting more than 48 hours or having frequent recurrence, can be annoying [4]. Persistent hiccups can be caused by numerous etiologies, such as central nerve system pathology, peripheral neuropathy involving vagus or phrenic nerve, psychological event, systemic etiologies like toxin, metabolic disease, or adverse reaction to drugs [5]. In addition, dopaminergic pathway probably engaged in the pathophysiology of hiccups for both causative and curative role of dopaminergic agonist (promipexole) and antagonist (perphenazine) had been discussed in the literature [6].

Amantadine, an antiviral agent to influenza A, has been known to have anti-parkinsonian effect. Its mechanism of action includes anticholinergic effect, antagonist of N-Methyl-D-Aspartate (NMDA) receptor, and up-regulation of dopamine activity by enhancing pre synaptic release and blocking postsynaptic re-uptake [7,8]. Due to the above mechanism, it is hypothesized to be a favorable therapy for enhancing conscious arousal through activating dopaminergic circuits which accounts for arousal, drive, and attention [8]. Adverse effects include dizziness, lethargy, anticholinergic effects, insomnia, as well as nausea and vomiting had been reported occasionally and the symptoms were usually mild and reversible [7].

In our patient, we used amantadine for enhancing conscious recovery. In the literature review, two review articles concluded that

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amantadine seemed to improve arousal when used in early stage (<=3 days) of a severe TBI [1], and might be beneficial in functional recovery in post-acute stage (>4 weeks) of moderate-to-severe TBI [2]. Another review article also commented that amantadine improved arousal in children and adolescents in low-responsive state post TBI [9]. In the preliminary, international multi-center, randomized placebo-controlled trial, the author denoted the capability of amantadine for accelerating conscious arousal and functional recovery in severe TBI patients during the 4-week treatment interval compared with placebo [8]. In the molecular level, a promising result was presented in research and demonstrated amantadine may be a target therapy for post-TBI cognition deficit by reversing the chronic decline in the DARPP-32 signaling cascade following TBI [10].

There were no common adverse effects of amantadine occurred in our patient, however, hiccups consistently to develop a short period after 100mg daily of amantadine therapy in the first time and when re-challenged 7 days later, which was relieved by either discontinuation of medication or tapering dose to 100mg every other day. In a review, it was summarized that hiccups can occur with Central Nerve System (CNS) lesions accounting the brainstem [5]. Some cases with persistent hiccups because of brain lesion in other locations were also reported [11,12]. However, there was no existing correlation between TBI and hiccups. In addition, he never developed any period of hiccups before TBI and during post-TBI hospitalization. Thus, the findings strongly suggest that there may be a correlation between use of amantadine and hiccups after traumatic brain injury. In the previous reports, amantadine had only been reported to treat hiccups rather than a causal role [4,13,14]. However, it was possible that some dopamine modulation agents can both cause or cure hiccups in different conditions [6]. Therefore, in this case we attribute the persistent hiccups to the dopaminergic effect of amantadine and the adverse reaction seems to be a dose effect of amantadine.

To the best of our knowledge, this is the first case reporting persistent hiccups secondary to amantadine for conscious arousal in a TBI patient. Hiccups could lead to some detrimental complications, thus we provide this unique experience for early recognition of etiology for persistent hiccups in such patients. Much effort should be done to establish the pharmaceutical effect of amantadine on hiccups.

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