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Case Report

High Blood Pressure Induced by the Rivastigmine Patch as an Uncommon Side Effect

Chien-Chung Huang [a], Chia-Ming Chang [a,b *], Hui-Ning Tu [c]

[a] *Division of Geriatrics and Gerontology, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan,* [b] *Institute of Gerontology, National Cheng Kung University Medical College, Tainan, Taiwan,* [c] *Department of Pharmacy, National Cheng Kung University Hospital, National Cheng Kung University, Tainan, Taiwan*

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SUMMARY

Aging has become an important issue in Taiwan, dementia and medication problems are important issues among older people. Alzheimer's disease (AD) is a common cause of dementia. A new treatment in the form of the rivastigmine patch (Exelon®) is used to overcome deficits in the cholinergic system of patients with AD. We report a case of an uncommon adverse effect of high blood pressure caused by increasing dosage of cholinesterase inhibitor (ChEI) and postulated that ChEIs increase arterial blood pressure by acting through central muscarinic receptor type 1 and type 2. Attentions of rare side effects and treatment of unwanted complications are crucial after the prompt recognition of the symptoms or signs of hypertension induced by the rivastigmine patch.

1. Introduction

Among older adults, Alzheimer disease (AD) is a worldwide health problem that causes functional disorders in memory, cognition, learning, behavior, and attention.[1–3] Cholinergic neurons are deficient in patients with AD.[2,3] Rivastigmine is a new-generation agent that compensates for the lack of acetylcholine secretion in AD.[2–5] The Food & Drug Administration approved the rivastigmine patch[6] in July 2007. However, the adverse drug reactions that occur in less than 5% of cases clinically are less attractive. The changes in blood pressure and heart rate induced by cholinesterase inhibitor (ChEI) have rarely been described.[7,8] We report a patient who exhibited cholinergic-associated symptoms of nausea, vomiting, and high blood pressure induced by the larger dose of rivastigmine patch.

2. Case report

The patient was an 83 year-old, 35.7 kg woman without other known underlying diseases in addition to AD. Because of slowly progressive memory and cognitive impairment since 2007, she was regularly treated with a rivastigmine patch in the neurology outpatient department (OPD). She was treated with rivastigmine patch (4.6 mg/24 h) for AD on April 10, 2016 because she was scored 53/100 down from 60 on the Cognitive Abilities Screening Instrument, and 12/30 down from 21 on the Mini-Mental State Examination since September 2014. However, she lost to OPD follow-up since November 11, 2016. On July 2017, she returned to receive a 4.6 mg/24 h patch for 30 days. Her dose increased to 9.5 mg/24 h on August 11, 2017.

By reviewing National Health Insurance PharmaCloud, this patient had no medication of hypertension before and had ever a visit at Family Medicine OPD on September 26, 2017, when she was found to have hypertension with 171/87 mmHg at that time. Antihypertension medication (Valsartan/hydrochlorothiazide 80/12.5 mg) as needed (prn) was prescribed by the family physician. On October 10, 2017, she suffered from nausea, vomiting, dizziness, and falling down and was sent to emergency room (ER). In the ER, her hypertensive emergency (blood pressure: 217/142 mmHg) was found. Her body temperature was 36.4 °C, pulse rate was 101 bpm, respiratory rate was 20/minute, and pulse oximetry was 100% while breathing ambient air. Other physical examinations, blood tests for complete blood count, and renal (creatinine level: 0.76 mg/dL, normal range, 0.50–0.90 mg/dL) and liver function (alanine aminotransferase: 13 U/L, normal range 15–30 U/L) findings were unremarkable. Concerning the fall, she underwent brain computed tomography which showed a suspected old fracture of the right maxillary sinus wall and right zygomatic arch. After immediate management with intravenous metoclopramide 10 mg, oral nifedipine 10 mg, diphenidol 25 mg, and simethicone 40 mg, she was discharged in a stable condition 4 hours later.

On October 12, 2017, she was followed up at the Geriatrics OPD for dizziness and high blood pressure. After discontinuing the rivastigmine patch in the following one-month visit and oral nifedipine 10mg prn was administered, her symptoms improved and her blood pressure returned within normal limits (within 80–110/60–70 mmHg). Afterwards, she was resumed with a lower dose rivastigmine patch (4.6 mg/24 h) without discomfort. We calculated the ADR probability

* Corresponding author. Division of Geriatrics and Gerontology, Department of Internal Medicine, National Cheng Kung University Hospital, No. 138, Sheng Li Road, Tainan 70403, Taiwan.
E-mail address: charming.tw@hotmail.com (C.-M. Chang)

using the scale designed by Naranjo et al.[9] in this patient, and found that the hypertension was a probable consequence of the rivastigmine patch (Naranjo score: 6). We strongly suspected that the relative excessive doage of rivastigmine from the patch might be related to the hypertension.

3. Discussion

Based on previous studies, the ADRs of rivastigmine patches are dose related.[6,10] The rate of hypertension as an adverse drug reaction (ADR) increased to 3.7% from 2.5% after increasing the dose (13.3 mg/24 h compared with 9.5 mg/24 h) in a 24-week double-blind treatment phase.[6,10] This ADR does not persist during weeks 24–48 of a treatment phase.[6] Nonetheless it is not unreasonable to recognize high blood pressure can be induced by larger dose rivastigmine patches. In mouse model, ChEIs were shown to act centrally, facilitating the low-frequency domains of blood pressure variability, like a pressor response.[8] The parasympathetic effect is potentiated and saturated which lead to an increase in sympathetic tone, and high blood pressure, especially during the diastolic phase. Central muscarinic type 1 (M1) and M2 activation were believed to trigger the high blood pressure in rat models.[7] Once the larger dose of rivastigmine is applied, the additional amount of rivastigmine via the altered metabolic process may induce unresolved saturation effect.[7,11] After the repeated exposure to the double dose, namely overdose proportional to exposure in the simulated concentration-time profiles, high concentration may occur.[11] Patients with ADRs displayed carbamate-like toxicity with cholinergic features of the muscarinic type, i.e., salivation and vomiting, and of the nicotinic type, i.e., hypertension when repeated high-dose rivastigmine patches were applied.[12,13]

Furthermore, the site application of a rivastigmine patch exhibits different pharmacokinetics. Application to the upper arm, chest, and upper back demonstrated better bioavailability than that to the abdomen and lateral thighs (i.e., the maximum concentration fluctuates).[14] Rivastigmine patch at a dose of 9.5 mg/24 h provides exposure comparable to the highest capsule dose (6 mg, twice daily).[15] It also has excellent pharmacokinetics with a peak plasma concentration of 8.7 ng/mL and slow absorption rate of 8.1 h.[4] However, the elimination half-life is 3.2–3.9 h,[13] the total elimination time is approximate 20 h. Whether the previous application of a rivastigmine patch affects the normal metabolic pathway remains unclear.[11]

In one study, high-dose rivastigmine patches (≥ 17.4 mg/24 h) were not recommended in the highly susceptible patients.[11] Even though the daily dose of the patch didn't exceed 17.4 mg/24 h, our reported case is an underweight (35.7 kg), old aged woman whose rivastigmine concentration might be higher. Based on the above description, the accumulated amount of rivastigmine in the human body can be related to occurrence of hypertension. Inconsistent conclusions of basic research existed concerning whether blood pressure increases as heart rate changes.[7,8] Although no clinically studies have examined the association between ChEIs and human blood pressure,[7] we present a case of use of the rivastigmine patch and resulted in hypertension, especially at a higher dose. Closely monitoring of blood pressure is recommended for patients using ChEIs.[7]

Declaration

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