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Case Report

Delirium Induced by Perindopril: A Case Report

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Introduction

Perindopril is a commonly prescribed angiotensin converting enzyme inhibitor because of its safety and efficacy [1]. Some of ACE inhibitors can cross blood brain barrier, and have the ability to cause neuropsychiatry effects [2]. Risk factors for ACE inhibitors-induced delirium include advanced age and underlying neuropsychiatry disorders [3]. In this case report, we present a case of a patient with delirium caused by perindopril.

Case Presentation

The patient was a 51 year-old female who is known to have a history of knee osteoarthritis and recently diagnosed with hypertension. She is on aceclofenac 100mg for knee osteoarthritis, and recently started on perindopril/amlodipine 10mg/10mg for hypertension. Patient brought in to emergency department to our facility with few hours history of strange behavior (ex. she does not remember names of her children, does not remember she had dinner). In the last two weeks, she has more pain in her left knee after physiotherapy; the patient was not sleeping at night for several days. The day prior to her presentation, she was doing well, slept at midnight. After two hours she wake up with severe left sided knee pain. She took the first dose of perindopril arginine/amlodipine 10mg/10mg with aceclofenac 100mg. On her way to our facility, patient had shaking movements of upper and lower limbs, lasted for two minutes, but there were no tongue bite, frothy discharges, up rolling of the eyes, or loss of consciousness. No weakness in limbs, dysarthria, or facial deviation. No history of similar event. Review of systems revealed pain and swelling in the calf of her left leg, no headache, no fever, no trauma, no chest pain, no breathing difficulty, normal bowel habits, and no urinary symptoms. On physical examinations, patient was awake, alert, oriented to person, place, and time, not oriented to date. Montreal Cognitive Assessment (MOCA) done on the day of her presentation 19/30 as shown in Figure 1. Carinal nerves, motor, sensory, reflexes and coordination systems were unremarkable. Examinations of other systems, including her cardiovascular, respiratory, gastrointestinal, and genitourinary systems, revealed unremarkable findings. Laboratory investigations showed normal electrolytes, normal renal function, no leukocytosis or leukopenia, no anemia, normal random blood glucose, normal thyroid function tests, normal vitamin B 12 level, D-Dimer was 0.550, urine dipstick was positive for nitrite & leukocytes esterase. CXR was unremarkable. CT Head, MRA Head & Neck were unremarkable. Aceclofenac and perindopril were discontinued, and patient kept on amlodipine 10mg. She was treated with amoxicillin-clavutanate acid for simple cystitis. Repeated Montreal Cognitive Assessment (MOCA) in the next day was 21/30 as shown in Figure 1. MRI brain, and electroencephalogram were unremarkable. Ultrasound of left lower limb did not show any evidence of vein thrombosis. MRI of left knee showed ruptured left Baker's cyst, and mild joint effusion. She was treated with celecoxib 200mg BID along with pantoprazole 40mg. A clinical diagnosis of perindopril and aceclofenac induced delirium was made. Patient discharged home in a good condition after four days. The patient came to the clinic after few weeks for follow-up, she was back to her normal life.

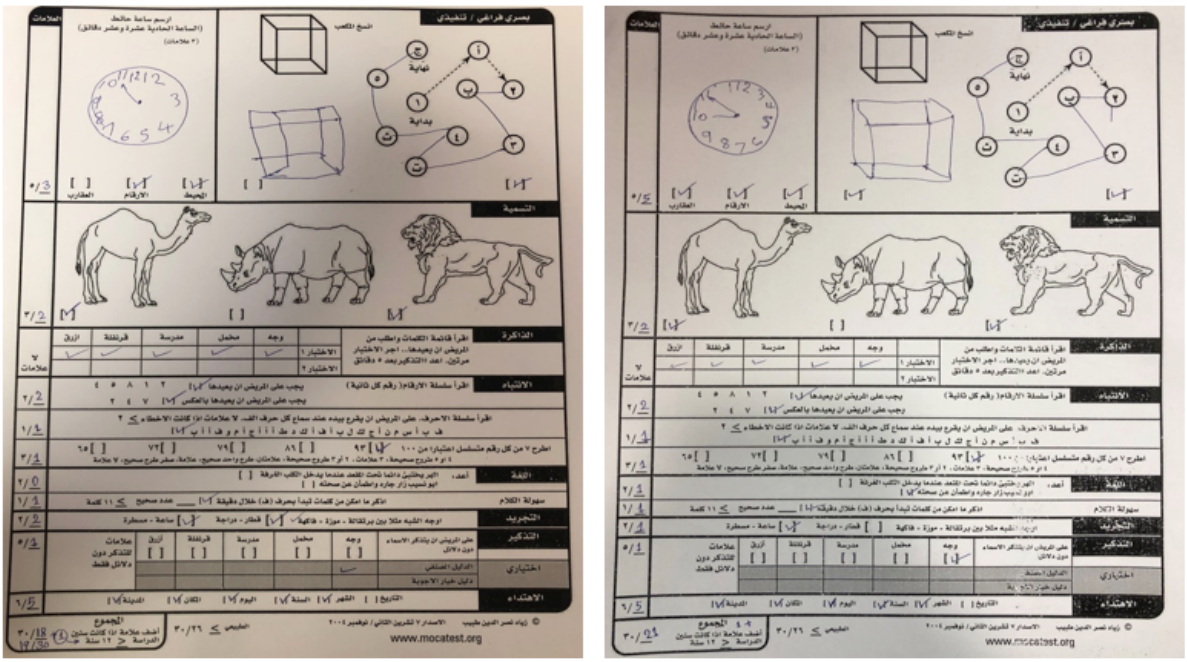

Figure 1: Montreal Cognitive Assessment (MOCA) on admission and next day.

Discussion

Perindopril is prodrug of perindoprilat, which acts as a competitive inhibitor of angiotensin converting enzyme, prevents conversion of angiotensin I to angiotensin II which in turn causes an increase in plasma renin activity, and reduction in aldosterone secretions [2]. It is play a major role in pathophysiology of vascular system, and acts on the brain as a neurotransmitters on different receptors that are associated with memory and learning [4]. Its onset of action apparent with in one to two hours, and its duration of action probably in the range of 3 to 10 hours [2]. There are two forms of perindopril; perindopril arginine which used in this case, and perindopril erbumine. Both of them have the same side effects profile [3]. The arginine salt has the advantage of being more stable at higher temperatures or humidity [3]. The most common side effects of perindopril include dry cough (10% to 20%), dizziness (12% to 19%), hypotension (7% to 11%), increased BUN and Cr (2% to 11%), syncope (5% to 7%), and hyperkalemia (2% to 6%) [1]. Perindopril can cross blood brain barrier, and cause neuropsychiatry effects [5]. Other ACE inhibitors that cross the blood brain barrier include captopril, fosinopril, lisinopril, ramipril, and trandolapril [5]. The acute confusional state that described in the above case could relate to the observation that brain ACE hydrolyzes opioid peptides; ACE inhibitor has been shown to inhibit the degradation of endogenous opioid peptides, thus raising their concentrations to potentially cause delirium [5]. This observation supported by a case report documenting reversible of ACE induced psychosis with naloxone [6]. Delirium developed within 2 hours to 6 years after initiation of an ACE inhibitor and resolved within 1 to 30 days after cessation [7]. Elderly patient with mild cognitive impairment or dementia at high risk to develop delirium induced by ACE inhibitors [7]. There are conflicting studies regarding the use of ACE inhibitors and their effect on memory. There is a study was reported in 2003 showed that the use of ACE inhibitor was associated with improved cognitive performance and lower risk of dementia [8]. Another study was done on animal models in 2008 showed similar results [9]. While other studies showed that ACE inhibitors are correlated with increasing of Aβ concentrations and the onset of dementia [4]. Due to conflicting results, there is a need to study the role of ACE inhibitors on cognitive performance.

Aceclofenac is a potent non-steroidal anti-inflammatory drug. The most common side effects of NSAIDs include gastrointestinal, renal, and cardiac events. There are several mechanisms of action for NSAIDs to cause delirium including stimulation of nitric oxide-cyclic guanosine monophosphate (NO–cGMP) pathway, inhibition of N-methyl-D-aspartate (NMDA)-receptor, inhibition of peroxisome proliferator-activated receptor gamma (PPAR)-γ, and effects on various cytokines [9]. Patient's symptoms in this case developed after few hours from starting perindopril arginine, and improved significantly after discontinuation. Patient was on aceclofenac since few weeks, and this is another possibility for the patient's symptoms. Amoxicillin is another medication that can

cause acute psychosis [7]. Symptoms occurred within 2 hours to 10 days after medication initiation and resolved completely upon discontinuation [7]. In this case, it's unlikely to be the cause as it was initiated after patient's symptoms started. The differential diagnosis for drug-induced delirium must include any condition that cause delirium such as acute infection, stroke, vasculitis, degenerative dementia and psychiatric diseases. There are no definitive tests to determine whether a patient is experiencing medication-induced delirium [7]. A thorough history and physical examination are needed to help establish the diagnosis. It is important to determine the onset of symptoms; medication-induced acute confusional state is usually related to an increase in dosage or changes to medication regimens, with symptoms appearing within days of drug initiation, dosage change, or discontinuation [7]. Medication-induced delirium should be considered in a patient older than 35 years with no known psychiatric history [7]. Certain medications can take longer duration to cause their side effects. If the patient's symptoms persist after discontinuation of medications for 4 weeks, then the patient will need further evaluation for the symptoms [7]. Drug-induced delirium is self-limiting, managed by discontinuation of offending agents, and if not possible then will need to lower the dose of medications or use antipsychotic medications to treat the symptoms [7]. Medications should be reported even if they have not associated with any side effects in the past, as they might interact with medications given in the hospital [10].

Conclusion

Many medications that act on the brain can cause delirium. Special care is needed when prescribing medications for people with cognitive impairment, especially in elderly patients as they are at high risk for developing this side effect. Early diagnosis of drug-induced confusion and discontinuation of the offending agent is essential. The findings from this case are expected to raise awareness about this side effect among health care professionals.

Competing interests: The authors declare that they have no competing interests.

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