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Possible heart failure associated with pregabalin use: case report

Pregabalin kullanımı sonrası gelişen muhtemel kalp yetmezliği: Olgu sunumu

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Summary

Pregabalin and gabapentin are widely used analgesic, anticonvulsant and anxiolytic agents as they are relatively reliable and easily tolerated. However, they may cause some side effects such as dizziness, somnolence, dose-dependent peripheral edema, and weight gain, which may cause patients to abandon their use. Furthermore, there are a few reports in the literature addressing elderly patients with serious chronic disease and cardiac history, who develop heart failure during pregabalin application. In this report, we present a patient with no cardiac history treated with 300 mg/kg pregabalin due to neuropathic pain, who developed peripheral and then central edema, which were determined after advanced investigations. After stopping pregabalin, the situation regressed. Then, peripheral edema developed associated with the recommended dose of gabapentin, which was used in place of pregabalin. Despite the lack of any published evidence, the New York Heart Association issued a warning about using caution when prescribing pregabalin to type III-IV heart failure patients. Though the effect mechanisms of pregabalin and gabapentin are not well known, the calcium channel relationship may lead to these side effects. In summary, we believe that pregabalin and gabapentin, which is mostly used nowadays, should be administered with care not only in patients with advanced cardiac pathology but also in all patients, due to the potential side effects.

Key words: Heart failure; edema; pregabalin.

Özet

Pregabalin ve gabapentin, göreceli güvenilirlikleri ve kolay tolere edilebilmeleri nedeniyle kullanım alanı giderek genişleyen antikonvülzan, analjezik ve anksiyolitik ajanlardır. Buna karşı, baş dönmesi, somnolans, doz bağımlı periferik ödem ve kilo artışı gibi yan etkileri ilaç kesilmesine neden olabilmektedir. Ayrıca, literatürde ciddi kronik hastalık öyküsü ve kardiyak öyküsü olan yaşlı hastalarda kalp yetmezliği geliştiğine dair az sayıda olguya rastlanmıştır. Bu yazıda, kardiyak öyküsü olmayan ve nöropatik ağrı nedeniyle 300 mg/gün pregabalin sonrası öncelikle periferik ödem ve sonrasında ileri tetkiklerde tespit edilen santral ödem tablosu gelişen bir hasta sunuldu. Pregabalin kesilmesi sonrası tablonun gerilediği gözlenmekle birlikte önerilen dozlarda başlanan gabapentinle de periferik ödem gelişmiştir. New York Kalp Cemiyeti sınıf III-IV kalp yetmezliği olan hastalarda pregabalin reçete edilirken dikkatli olunması konusunda uyarmıştır. Etki mekanizmaları henüz netlik kazanmamış olmakla birlikte kalsiyum kanalları üzerindeki etkileri bu yan etkilerle ilişkili olabilir. Sonuç olarak, giderek artan hızda kullanılan bu ilaçların yan etkiler açısından ileri kardiyak hastalar dışında da yakından takip edilmesi gerektiği kanaatindeyiz.

Anahtar sözcükler: Kalp yetmezliği; ödem; pregabalin.

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Introduction

Pregabalin and gabapentin are similar compounds with analgesic, anticonvulsant and anxiolytic characteristics. Owing to such pharmacological features, they are commonly used throughout the world in neuropathic pain treatment and anxiety disorders. [1] In addition to these, the number of publications reporting their use in other areas such as postoperative analgesia and fibromyalgia is also on the rise.[2,3]

Many comprehensive and randomized controlled studies of high quality have shown the reliability and efficiency of pregabalin and gabapentin in neuropathic pain treatment, thus making them the first option in such treatment. The greatest advantages of these drugs have been listed as their relative reliability, easy use, high tolerance, and lack of negative interaction with other drugs.[1]

Slight and moderate side effects, such as dizziness and somnolance, in central nervous system are major factors for terminating the use of pregabalin. At the same time in some studies dose dependent usage of pregabalin induced peripheral edema and weight gain in 5-20 % and 4-12 % of patients, respectively. [4] Moreover, few studies have also reported a possible association between pregabalin use and chronic heart failure decompensation.[4-6] This article presents a case of heart failure after pregabalin use, despite the existence of previous cardiac history.

Case Report

A-54-year-old female patient presented to our Pain Clinic with a burning sensation and back pain. Her back pain had started after the bilateral thoracic sympathectomy in which she had undergone 2 months before, advanced through the left arm, and was continuous and strong. In the physical examination, incision scar at left thoracotomy and allodynia at 3rd and 4th thoracic dermatomes were identified. The patient reported to have used nonsteroidal anti-inflammatory drugs against pain but did not achieve any outcome. In addition, she did not have any previous history of a chronic disease or medication; was recommended inhaler salbutamol for short-term dyspnea only in the postoperative stage; and had stopped using it when the need disappeared.

Together with these findings, she was diagnosed as intercostal neuralgia and initially approached to have a medical treatment. The treatment started with 150 mg/day pregabalin for first week, continued with 300 mg/day in the second week. The starting dose of tramadol 37.5 mg/day was increased gradually; and a follow-up was recommended 2 weeks later.

The patient came for follow-up on 17th day of treatment and reported swelling in hands and ankles which started 3 days ago. During extremity examination, 2 positive pretibial edema was determined. The patient was admitted to the Pain Clinic for the side effect follow-up and pain palliation. The peripheral edema was initially attributed to pregabalin and the usage of drug was stopped. The blood examination showed that electrolyte, blood urea nitrogen and creatinine levels were within normal limits and glomerular filtration speed was 86.88 ml/min/1.73. For the continuing pain, tramadol was given via patient-controlled analgesia (PCA) (bolus 6 mg, lock-out time 10 min, 4 hr limit 60 mg). After determining daily tramadol requirement, oral tramadol retard 100 mg was added to the analgesic medication, and PCA was stopped on day 3. On follow up, hemodynamic parameters were stable. In addition, inhaler salbutamol was given again for the occasional slight dyspnea. At the end of one week, the patient was discharged with pain palliation, reduced peripheral edema, and tramadol retard 200 mg/daily medication. After discharge, she was recommended to visit the Internal Medicine Polyclinic for follow-up.

The patient was examined by thorax computed tomography scan (CT), which was requested by the Internal Medicine Polyclinic. According to that, cardiomegalia, appearance of pericardial fluid, additionally pleural fluid at the base of both hemithorax even more significant on the right were revealed. After CT results only diuretic treatment has begun and in the third day of treatment echocardiography results showed 76% ejection fraction and no pathological findings other than pleural effusion. In the follow-up thorax CT performed 15 days after stopping pregabalin, cardiomegalia and pericardial fluid had disappeared and only minimal pleural effusion was seen. Peripheral edema had regressed and the complaint of dyspnea had disappeared.

The patient reported reduced but persisting pain, upon which 300 mg/day gabapentin started and was increased to 900 mg/day with close follow-up. However, due to the edema that developed approximately 20 days later, gabapentin was stopped and analgesia was achieved only with tramadol. The edema due to gabapentin was also followed up closely and regressed on day 3.

Discussion

In our patient peripheral edema developed on 14th day of treatment with 300 mg/day pregabalin. Since no other chronic disease history and medication were present to explain the peripheral edema, pregabalin was initially held responsible and stopped to use. Due to the existing postoperative story of the patient, we did not associate dyspnea with this picture initially. Upon the lack of an abnormality in hemodynamic parameters and kidney function tests, and the regression in peripheral edema, we did not require further examinations or treatment. However, the thorax CT led to the conclusion that pregabalin causes central as well as peripheral edema. The lack of a cardiac etiological factor corroborated our view.

The side effects of pregabalin was investigated by using Naranjo algorithm. Accordingly, the drug scored 7 on the Naranjo algorithm and accepted as having potential side effects.[7]

A few case reports have claimed an association between pregabalin and chronic heart failure decompensation.[4-6] Unlike to our patient, those reported in these studies had low ejection fraction and multiple chronic disease histories classified as stage II-III in the New York Heart Association classification.

Page et al. has reported the possible association between pregabalin administration and chronic heart failure decompensation in their 3 separate cases. In one of their cases, they used 600 mg/day gabapentin instead of pregabalin and reported an improvement on patients neuropathy without worsening of clinical status.[4] However, gabapentin is claimed to induce peripheral and central edema with doses exceeding 1800 mg/day, and caution is recommended when it is used instead of pregabalin in the chronic pain treatment of patients with heart failure.[8,9] As our patient did not favor interventional methods and had persistent complaints, we administered gabapentin under close follow-up and increased the dose according to patient response. However, peripheral edema was observed during the third week of 900 mg/day gabapentin treatment.

American Food and Drug Administration has issued a warning about hypotension and peripheral edema that pregabalin may cause, particularly when used in combination with thiazolidinedione. Further, despite the presence of any published evidence, NYHA also issued a warning about being careful when prescribing it to type III-IV heart failure patients.[10] No such warning has been issued by the European Medications Evaluation Agency.

The effect mechanisms of pregabalin and gabapentin are not well known. Previous studies claimed that they show their analgesic effects by binding to α2-δ type 1 and 2 subunits of voltage dependent the calcium channels and by reducing potassium dependent the calcium entry. The effects of α2-δ type 1 and 2 subunits on calcium channel functions and conventional calcium channel subtypes are not clear.[11] Stefani et al. assert that gabapentin may affect L-type calcium channels.[12] This calcium channel relationship may lead to peripheral edema with peripheral vasodilation and fluid leak into the interstitial area. It is thought that quick and unexplained weight gain may be a sign of fluid retention, which may exacerbate congestive heart failure.[13,14]

In this case report, we presented the development of heart failure in a patient without previous cardiac pathology after normal dose pregabalin use. In summary, we believe that pregabalin, which is mostly used nowadays, should be administered with care due to its potential side effects, and in cases of edema or heart failure associated with pregabalin use, gabapentin should be considered under caution.

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