

Pregabalin-Induced Heart Failure: A  
New Entity?

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## Abstract

Pregabalin is a drug widely used in patients with neuropathic pain. While it may cause common adverse events such as dizziness, somnolence and peripheral edema, there are a few reports addressing a possible relationship between pregabalin and heart failure. Here we report an elderly woman with a history of heart failure New York Heart Association (NYHA) class I who was taking pregabalin presented with acute decompensated heart failure and acute kidney injury. With discontinuation of pregabalin and supportive treatment, patient's symptoms improved rapidly and she was discharged well. Though exact mechanism is still unclear, it is believed that antagonism of the L-type calcium channels in vasculature plays a role in pregabalin induced heart failure. Current American Heart Association (AHA) guideline recommends prescribing pregabalin with caution in patients with NYHA class III to IV heart failure. From this case report, we would suggest to use pregabalin cautiously in all patients with history of heart failure (NYHA class I to IV) especially when there is co-existing renal impairment.

## Introduction

Pregabalin is commonly used as an antiepileptic, analgesic and anxiolytic drug. Pregabalin, like gabapentin, is a structural analogue of the inhibitory neurotransmitter  $\gamma$ -Aminobutyric Acid (GABA) [1]. Although the mechanism is not fully understood, it is hypothesized that pregabalin binds to the  $\alpha 2$ -delta ( $\alpha 2$ - $\delta$ ) subunit in voltage-gated calcium channels in the presynaptic neurons, and therefore decreases the release of the excitatory neurotransmitters [2]. Somnolence and dizziness are known side effects of pregabalin. Meta-analysis of randomized controlled trials of pregabalin has also shown a two fold increase in incidence of peripheral edema (15%), which can be associated with heart failure [3,4]. Peripheral edema may be attributed to the antagonism of the L-type calcium channel in the vasculature causing vasodilatation [5]. In addition, pregabalin is commonly prescribed to diabetic patients, who are more predisposed to heart failure due to concomitant renal or cardiac diseases. This article reports a case of heart failure after one week of pregabalin use.

## Case Report

A 71 year old female patient presented with acute onset of drowsiness and breathlessness for two days. She had a history of atrial septal defect which was repaired many years ago, but subsequently complicated by the development of pulmonary hypertension and congestive heart failure [New York Heart Association (NYHA) class I]. Furthermore, she had a history of atrial fibrillation and type 2 diabetes mellitus. Her regular medications included frusemide 40 mg twice a day, ivabradine 7.5 mg twice a day, sildenafil 5 mg three times a day, sitagliptin 100 mg once daily, pantoprazole 40 mg once daily, fenofibrate 145 mg once daily, montelukast 10 mg tablet every night, lovastatin 20 mg once every night, spironolactone 25 mg once daily, and warfarin sodium 1 mg every morning. The patient had a recent admission two weeks ago due to severe lower back pain from compression fracture, for which she was prescribed regular tramadol 50 mg three times a day upon discharge. One week later, she was started on pregabalin 50 mg 3 times a day due to poorly controlled back pain. On admission, the patient was noted to have bilateral lower limb pitting edema and bilateral lung crepitations. Her chest X ray showed cardiomegaly with pulmonary congestion, Arterial Blood Gas (ABG) showed hypercapnic respiratory failure, with a B-type natriuretic peptide level of 442 pg/ml. She also had a raised creatinine level on admission of 187  $\mu$ mol/L with no history of chronic kidney disease. The diagnosis was acute pulmonary edema complicated with acute kidney injury. Subsequently, the patient was started on intravenous diuresis, intubated and mechanically ventilated. Pregabalin was also stopped since admission. The patient improved rapidly with treatment and was successfully extubated three days later. On day 4 of admission, an echocardiography showed an ejection fraction (EF) of 65%, atrial septal defect with residual flow from post repair, moderate mitral valve regurgitation and mild pulmonary hypertension. On day 5, the patient's pulmonary edema fully resolved and her renal function was much improved as well (creatinine level improved to 91  $\mu$ mol/L upon discharge). She was comfortable on room air and able to ambulate with physiotherapist assistance. She was then discharged home for follow-up with her cardiologist and counselled to stop taking pregabalin.

**Table 1:** The Naranjo adverse drug reaction probability scale.

	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event occur after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0
			Total	6

## Discussion

Pregabalin, a GABA analogue, is approved for the treatment of pain from diabetic neuropathy and post-herpetic neuralgia, anxiety disorders, and also as an adjunctive therapy of partial seizures in adults. It has been found that pregabalin binds to  $\alpha 2\text{-}\delta$  subunit of voltage-gated calcium channels, thereby inhibiting excitatory neurotransmitter release [1]. In the animal hypertension model, there is evidence that an increase in  $\alpha 2\text{-}\delta$  subunits of the calcium channels is associated with vasoconstriction. Hence, pregabalin can potentially cause vasodilatation and fluid retention via inhibition of the  $\alpha 2\text{-}\delta$  subunit in the heart and vasculature [6]. There is also a case report about complete atrioventricular block due to an overdose of pregabalin which also suggests that pregabalin can inhibit the L-type calcium channels in myocardium as well [7]. While American Heart Association (AHA) cautions use of pregabalin in patients with NYHA class III to IV heart failure due to the risk of peripheral edema and heart failure exacerbation, there are also recent case reports of patients with NYHA class I to II exhibiting similar symptoms [8,9].

The most common precipitants of acute decompensated heart failure include noncompliance, uncontrolled hypertension, ischemia, arrhythmias, infection, or drugs which are known to cause heart failure like calcium channel blocker [10]. However, in this case, the cause of acute decompensated heart failure was not clear at the beginning. The patient was compliant to her usual medications and fluid restriction. Her systolic blood pressure on admission was below 160 mmHg. There was no evidence suggestive of acute coronary syndrome based on electrocardiogram and cardiac enzymes. Though she had a history of atrial fibrillation, her ventricular rate was relatively well controlled with the fastest rate was at 114 beats per minute on admission. But her heart rate decreased to below less than 100 beats per minute six hours later when her condition stabilized. There was also no clinical suspicion of any infection that can possibly precipitate heart failure. On day 2 of admission, the possibility of pregabalin induced heart failure was considered when patient's caregiver shared that patient was recently started on pregabalin for pain control. After withdrawal of pregabalin on admission, the patient recovered rapidly with supportive treatment. Naranjo algorithm was used to investigate the

side effects of pregabalin [11]. In this case, the drug scored 6 (Table 1), which indicates potential side effects.

Furthermore, this patient was noted to have acute kidney injury on admission. Her baseline renal function was normal, but her admission creatinine level was 187  $\mu\text{mol/L}$  with a Glomerular Filtration Ratio (GFR) of 23 mL/min, in which the recommended renal adjusted pregabalin dose is 25-50 mg once daily. As pregabalin is primarily excreted through the kidneys, an overdose of pregabalin (50 mg 3 times a day) in this patient may have contributed to her early onset of decompensated heart failure, while in other case reports decompensated heart failure usually occurs weeks after starting pregabalin. Pregabalin is also dialyzable as it has a low molecular weight, a low volume of distribution and is not protein bound. Yoo L et.al. (2009) reported a case of a dialysis patient who developed myoclonus secondary to an increase in pregabalin dose which resolved immediately after dialysis. This suggests a potential role of dialysis in the reversal of pregabalin toxicity [12]. In this case, dialysis was not started as the patient responded well to supportive treatment, especially diuretics.

Overall, the exact mechanism of pregabalin-induced decompensated heart failure is still not clear [13]. There have been no large retrospective or prospective trials done to review the incidence of pregabalin induced decompensated heart failure. Ho et.al. (2013) is conducting a systemic review about the risks of developing heart failure with the use of pregabalin, which may give us a clearer understanding of pregabalin induced heart failure [14]. From previous case reports and this current case report, we would recommend that pregabalin should be prescribed with caution in patients with a history of congestive heart failure (NYHA Class I to IV), especially if there is existing renal impairment.

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