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Does Sibutramine Increase Tendency For The Development of Pneumonia?

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Abstract

40 years old male patient was admitted to the Emergency Department with the typical complaints of pneumonia. Physical examination, laboratory, radiological findings were consistent with community-acquired pneumonia, and the case's systolic pulmonary artery pressure was 38 mmHg. The case had no predisposing factors and co-morbidites regarding the pneumonia except six months sibutramine therapy for weight loss. Sibutramine, a combined serotonin and norepinephrine reuptake inhibitor, had some side effects including bronchitis and dyspnea. Therefore, the aim of this report is to consider sibutramine serotonergic action mechanism due to may cause pulmonary hypertension, and it may increase the tendency for pneumonia.

Key words: Anti-obesity agents, obesity, pneumonia, sibutramine

Introduction

Obesity is characterized by excess body fat, and is an important health problem in the world. It is defined that body mass index (BMI) equal to or greater than 25 kg/m^2 is overweight and greater than 30 kg/m^2 is obese (1, 2). According to WHO (2008), approximately 10% of adults were obese in theworld. The obesity complications are substantial and have the risks of dyslipidaemia, hypertension, cardiovascular disease, type 2 diabetes, obstructive sleep apnea, and several cancers. Avarege life expectancy is reduced due to obesity (3, 4).

Lifestyle and behavioral modification, diet, and exercise are initial treatment methods for the disorder. Medical therapy is recommended for obese or overweight patients who have co-morbidities such as type 2 diabetes, hypertension, and dislipidemia. The drugs for obesity are divided into three groupsin related to the action mechanisms; inhibitors of fat absorption, appetite suppressants, stimulators of energy expenditure and thermogenesis (3, 5).

Sibutramine, a combined serotonin (S) and norepinephrine (NE) reuptake inhibitor, is used in the treatment of obese cases need pharmacotherapy as a part of a multidisciplinary approach for weight loss. It ameliorates insulin resistance markers, carbohydrate metabolism, and atherogenic lipid disorders in both diabetic and nondiabetic patients, most of these effects are due to weight loss (6).

The most common adverse effects of sibutramine consist of dry mouth, constipation, insomnia, headache, anorexia and nausea. They can be attributed to the anticholinergic action of this drug. Several additional side effects have been revealed in 1% of all cases who had sibutramine in pre-marketing researchs. These include fever, diarrhea, gastroenteritis, tooth disorder, peripheral edema, hypertonia, bronchitis, and dyspnea. Moreover, several

cardiovascular events (hypertension, tachycardia, arrhythmias, and myocardial infarction) were reported in patients with treated by sibutramine. This led to a contraindication of the use of the drug in cases with coronary heart disease, previous stroke, heart failure, or cardiac arrhythmias (6, 7).

Community-acquired pneumonia(CAP) is associated with morbidity and mortality, and a globally important health problem. CAP is a potentially life-threatening illness, and the identification and treatment of the patients presenting with pneumonia is a major challenge for physicians (8). Co-diseases consisting heart, diabetes mellitus, chronic lung, renal disease, immunosuppressing conditions, and malignancies predispose CAP and complicate the disorder (9).

Here, we present a case who is admitted to the emergency department with typical symptoms and signs of pneumonia. The patient was diagnosed as CAP, and had empirical antibiotic therapy. The case had no predisposing factors and co-morbidites regarding the pneumonia except six months sibutramine therapy. Nowadays, because of the adverse effects, the sibutramine therapy for obesity is limited all over the world. Therefore, the aim of this report is to consider this probable relation in aspect of the tendency for pneumonia due to sibutramine therapy.

Case Report

40 years old male patient was admitted to the Emergency Department with the complaints of fever, cough, sputum, pleurotic chest pain and shortness of breath. The case had these complaints for one week, and these findings became more severe for the last two days. In the past history, he had sibutramine therapy (10 mg/day) for six months and lost approximately 10 kg. The case had no predisposing factors and co-morbidites regarding the CAP.

In the physical examination, the patient's BMI was 33.95 kg/m^2, the body temperature was 39.3 ºC, the pulse and respiration rates were 120 and 20 per minute, respectively. There were dullness, inspiratory crackles, and weakness of respiratory sound during auscillation at the basal region of the left lung. Other findings were normal. The labarotory results revealed leucocytosis, and increased serum CRP level. The patient's sputum culture was negative.

The chest x-ray displayed blunting ofthe left costophrenic sinus. Thorax CT showed that there was pleural effusion which is located at the inferior basal segment of left lung and extends to major fissure, and the thickest part of the effusion was 5 mm. There was a patchy consolidation at the posterobasal segment of left lung (figure 1,2). In echocardiographic examination the case's systolic pulmonary artery pressure was 38 mmHg, and other findings were within normal limits.

The patient was diagnosed as CAP complicated with parapneumonic effusion. Empirical antibiotic regimen was started, and the drug therapy was given for 2 weeks. The case had also mucolytic expectorants, nonsteroidal anti-inflammatory drugs. The complaints of the patient were resolved after first week of the treatment.

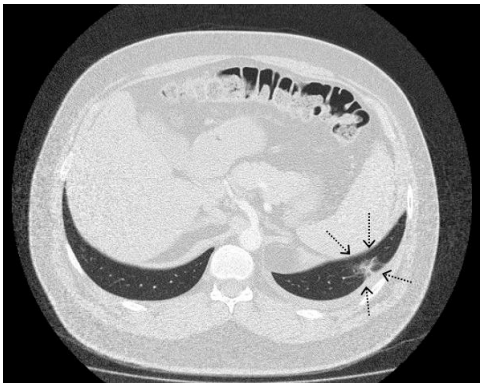

Figure-1. Thorax CT showing patchy consolidation at the posterobasal segment of left lung (black dotted arrows).

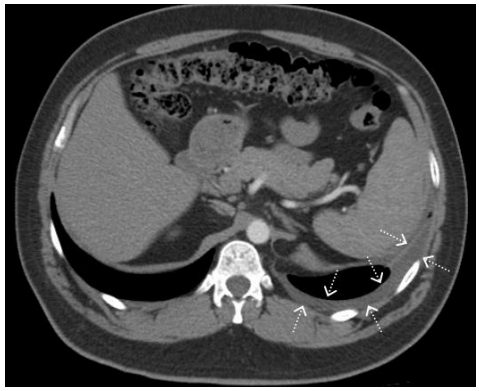

Figure-2. Thorax CT displaying pleural effusion located at the inferior basal segment of left lung, and the thickest part of the effusion 5 mm (white dotted arrows)

Discussion

CAP is a commonly occurring serious disorder and is the first infectious cause of death and the sixth cause of overall mortality in the developed countries (10). Identifying predisposing factors and implementing strategies in reducing the exposure to changeable conditions may decrease mortality and morbidity. Risk factors that are related with CAP include age, smoking, malnutrition, previous hospital admission, previous pneumonia, upper respiratory tract infection history, the upper respiratory tract interventions including nasogastric tube, and bronchoscopy, diabetes mellitus, heart disease, chronic bronchitis, chronic obstructive pulmonary disease, asthma, chronic renal failure, cancer, dental prosthesis, and aspiration. Several studies show that some forms of medical therapy may increase the risk of pneumonia. Treatment with digoxin, amiodarone, diuretics, N-acetylcysteine, xanthines, oral steroids, inhaled steroids, inhaled b-agonists and inhaled anticholinergic drugs were risk factors for the disorder. Current use of some antipsychotic drugs is shown to increase the risk of CAPin the

older patients by 2.1 times in a case-control study. The proton pump inhibitor therapy significantly enhances the risk of CAP by 50% to 89% (11, 12).

Obesity has controversial risk factors with regard to development of pneumonia, and there are many conflicting reports regarding obesity and pneumonia formation (13-15). Furthermore, in some papers, obese peoples may have increased sensitiveness to such as pneumonia due to changed ventilation pattern, reduced lung volume, augmented airway resistance, and increased risk of aspiration (15, 16). Also, the development of pneumonia in patients with obesity may be correlated with the level of BMI.

Sibutramine is a monoamine reuptake inhibitor that is achieved by augmenting central nervous system concentrations of monoamine neurotransmitters, such as dopamine (DA), NE, and S. It provides sustained weight loss by reducing food intake and enhancing energy expenditure. Sibutramine and its metabolites change serotonergic and noradrenergic, but not dopaminergic, activity in appetite control brain areas (17).

Fenfluramine that is structurally similar to *d*-amphetamine is a more powerful anorectic agent and it has no abuse potential. Dexfenfluramine is an active enantiomer of fenfluramine. The main mechanism of dexfenfluramine is due to release S (and to a much lesser extent NE). Fenfluramine, dexfenfluramine, and *d*-amphetamine are monoamine-releasing agents. Dexfenfluramine also has actions to enhance energy expenditure. Fenfluramine and dexfenfluramine was approved in 1973 and 1996, respectively as medications for the treatment of obesity in the US. They were widely prescribed and used in the long-term management of obesity. However, pulmonary hypertension (PH) and valvular heart disease were important adverse effects of this medical therapy. These drugs may result in pulmonary hypertension due to vasoconstrictor action of serotonin or by changing the depolarization of

pulmonary vascular smooth-muscle membrane. Then, these two drugs (fenfluramine and dexfenfluramine) were withdrawn from the market due to important adverse effects in 1997 by the FDA's recommendation (17, 18).

There is a tendency for pneumonia in the patients with PH (19, 20), and the mortality rate due to pneumonia is 7%. Influenza and pneumococcal vaccines are recommended for the cases with PH (19, 20). The old drugs (fenfluramine and dexfenfluramine) were withdrawn from the theraupetic usage in case of PH and valvular heart disease. The serotoninergic action mechanisms as anorectic agents are important for these drugs and sibutramine, and the mechanisms regarding serotonin might cause PH. In pre-marketing researches of sibutramine, it was revealed that the drug had some side effects including bronchitis and dyspnea. Therefore, sibutramine may result in PH, and it may increase the tendency for the development of pneumonia as in our case.

In the current study, we present a CAP case associated with parapneumonic effusion. The patient had any history of a predisposing factor for pneumonia. He had sibutramine therapy due to obesity for six months. During this period, the BMI decreased to 34 from 37 kg/m^2. The patient had no predisposing factor in terms of immunosuppressive conditions and drug therapy rather than use of sibutramine. Obesity is very important health problem all over the world and has many complications including type 2 diabetes, hypertension, cardiovascular disorders, etc. The conservative therapy consisting diet and exercise therapy is not usually effective, and sometimes, the patients with obesity need pharmacotherapy. Nowadays, obesity drugs are commonly used for the treatment. Unfortunately, they have many adverse effects, and some of them are life threatening. So, these drugs should be used very carefully, and the patients should be followed up closely.

To our knowledge, there was no study investigating the tendency for CAP regarding sibutramine therapy. Therefore, the aim of this report is to consider this probable relation in aspect of the tendency for development of pneumonia due to sibutramine therapy.

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