

Sudden Death from Pulmonary Hypertension in a Depressed Patient: a Case Report

一名抑鬱症患者因肺動脈高血壓猝死的個案

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Abstract

Duloxetine and mirtazapine are antidepressants used commonly in clinical practice. The former is a relatively new serotonin and noradrenaline reuptake inhibitor while the latter belongs to the group of noradrenergic and specifically serotonergic antidepressants. This case report describes sudden death in a patient with depression who was prescribed duloxetine and mirtazapine concomitantly. The cause of death was pulmonary thrombotic arteriopathy.

Key words: Pulmonary hypertension; Duloxetine; Mirtazapine

摘要

Duloxetine及mirtazapine普遍作為臨床抗抑鬱藥。Duloxetine是一種較新的5-羥色胺及去甲腎上腺素再吸收的抑制劑，而mirtazapine則屬於正腎上腺素組別及特異性5-羥色胺抗抑鬱藥。本文報告一名抑鬱症患者，同時服用duloxetine及mirtazapine後猝死的個案，死因為肺小動脈原位性血栓。

關鍵詞：肺動脈高血壓、Duloxetine、Mirtazapine

Introduction

Duloxetine is a well-tolerated and effective acute treatment for major depressive disorders that reduces painful physical symptoms.^{1,2} It has also found to be effective, safe, and well tolerated as a long-term treatment.³ Duloxetine has a side-effect profile similar to that of paroxetine except that insomnia is more frequently reported by patients using duloxetine.⁴ Hypertension is not a side-effect of either treatment. One study found that duloxetine had modest effects on the heart rate and blood pressure but no clinically meaningful effects on the electrocardiograms of a relatively healthy cohort of clinical trial patients. Duloxetine's cardiovascular effects appear to be comparable with those of medications considered first-line options for depression.⁵ Major treatment emergent adverse effects (those with an incidence of greater than 5% and significantly greater than placebo) are nausea, dry mouth, constipation, insomnia,

dizziness, fatigue, somnolence, increased sweating, and decreased appetite. Documented mean changes in blood pressure and heart rate are small.⁶

Mirtazapine has a mode of action differing from all other antidepressants. It increases noradrenergic and serotonergic neurotransmission via a blockade of the central alpha2-auto and hetero-adrenoceptors. The increased release of 5-HT, via increased cell firing of serotonin neurones, stimulates only the 5-HT1 receptors. 5-HT2 and 5-HT3 receptors are specifically blocked by mirtazapine.⁷⁻⁹ In several short-term clinical studies (i.e. over 5-6 weeks), mirtazapine demonstrated significant antidepressant effects as early as 1 week after starting treatment.¹⁰⁻¹² One study compared mirtazapine with selective serotonin-reuptake inhibitors (SSRIs), and found that mirtazapine had an earlier onset of action — with effects evident by week 2 — compared with citalopram.¹³ Another study revealed a significant reduction in Hamilton depression rating scale scores in patients taking mirtazapine compared with those on paroxetine at week 1.¹⁴ It is an effective and fast-acting antidepressant now used widely in psychiatric practice.

It is not uncommon for clinicians to combine 2 different groups of antidepressants to augment their effects, especially in patients who are not responding well to monotherapy. The combined use of mirtazapine and duloxetine is not well documented in the literature, thus their potential drug-drug interaction cannot be ruled out.

Pulmonary hypertension is an increase in pressure in

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the pulmonary artery, vein or capillaries (together known as the lung vasculature), leading to symptoms like shortness of breath, reduced exercise tolerance, dizziness, syncope, fatigue, non-productive cough, angina pectoris, peripheral oedema and, rarely, haemoptysis. It can be primary (idiopathic) or secondary and the latter is more common than the former. Medical conditions that may lead to secondary pulmonary hypertension include pulmonary emboli, emphysema, sickle-cell anaemia, connective tissue disease, sleep apnoea, congenital heart disease, cirrhosis, AIDS, lupus erythematosus, pulmonary fibrosis, and left-sided heart failure. People who climb to high altitude are at risk of developing a temporary form of pulmonary hypertension. A history of exposure to drugs such as cocaine, fenfluramine (a weight-reduction agent), methamphetamine, alcohol, and tobacco should also be sought. Older adults are more likely to have secondary pulmonary hypertension while younger people are more likely to have primary pulmonary hypertension. A family history of pulmonary hypertension (primary or secondary) is also a risk factor. Pulmonary hypertension is notoriously difficult to diagnose early as its signs and symptoms mimic those of other heart and lung conditions.

In 2006 an increased risk of persistent pulmonary hypertension of the newborn (PPHN) was found to be associated with in-utero exposure to SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) especially during the third trimester. The first study to describe this association, derived from a case control study using data from a birth defects database, reported that in-utero SSRI exposure after the 20th week of gestation was associated with an increased risk of PPHN (about 6-fold higher), with an absolute risk approaching 1%.¹⁵ A strong association was found between PPHN and several common prenatal and perinatal factors, including delivery by caesarean section, high maternal body mass index, being African American or Asian, and being large for gestational age. More recently, the association between SSRI and PPHN was readdressed in a case-control study using data from the Swedish Medical Birth Register of over 800,000 infants born between 1997 and 2005.¹⁶ A total of 506 infants had a discharge diagnosis of PPHN. The risk of PPHN associated with maternal use of SSRI among babies born after 34 weeks' gestation was increased by 2.4, after adjusting for other risk factors. These results are consistent with the 2006 study,¹⁵ but suggest a more attenuated risk and might explain why clinicians with patients treated with SSRI during pregnancy rarely see this condition. Nonetheless, even if there is an increased risk, the increase is small.

Case Report

A 48-year-old housewife first attended the West Kowloon Psychiatric Centre (WKPC) on 6 June 2007 after referral by the Lady Trench General Outpatient Clinic for suspected depression. She presented complaining of a depressed mood for around 1 year. She described being battered by her

husband in May and June 2006, which had upset her very much. Her symptoms included nightmares, headaches, sleep disturbance, poor appetite, reduced body weight, feelings of being followed by people, and fleeting suicidal ideas of burning charcoal (though she had never attempted suicide). She also had muddled thoughts and poor concentration. She gave a medical history of osteophytes on her left leg, managed with non-steroidal anti-inflammatory drugs such as ibuprofen and naproxen. She was otherwise medically fit and had no history of substance abuse. A full blood count, liver and renal function tests, thyroid function tests, and an electrocardiogram were performed. All were normal.

She was diagnosed as suffering from a moderate depressive episode and was referred to a medical social worker to manage her social problems. Medically, she was treated with mirtazapine 30 mg at night and zopiclone 7.5 mg before sleeping, when necessary. As her mood did not show significant improvement, the mirtazapine was increased to 45 mg at night on 15 August 2007.

On 10 October 2007, she complained of poor sleep despite taking her medications. She told the case doctor that she sometimes took 2 tablets of zopiclone at one time, despite being prescribed 1 tablet at night only. To manage her sleeping problems, thioridazine 50 mg at night was added as a hypnotic. She was not clinically suicidal. Her other medications were not changed. Her last visit to the WKPC was on 5 December 2007. She was subjectively dismal and had negative thoughts. She was not sleeping well because her sleep was disturbed by nightmares from time to time. She also complained of a pounding heart, irritability, and fearfulness. In view of this, the thioridazine was stopped and the zopiclone increased to 11.25 mg (1.5 tablets) before sleeping, when necessary. She also complained of multiple body aches so a trial of duloxetine 30 mg every morning was added for dual purposes: mood and pain alleviation.

The patient was admitted to a general hospital on 8 December 2007, 3 days after her last psychiatric consultation, with dizziness after using the toilet that led to syncope for seconds. There was no history of a drug overdose. She had no incontinence, post-ictal drowsiness, tarry stools, epigastric pain, or chest pain. On physical examination she was found to be afebrile with a blood pressure of 100/60 mm Hg, a pulse rate of 70-90 beats/min. The Glasgow Coma Scale was full and she was walking around normally. No cerebellar signs or focal neurological deficits were found and she had no murmurs or carotid bruits. Her abdomen was soft and non-tender, her chest was clear and she had a mild superficial laceration in the occipital region. An electrocardiogram showed sinus rhythm, with T wave inversion at V1-4, and a heart rate around 78 beats/min. Her chest X-ray was clear and showed no pneumothorax; a computed tomographic scan of her brain was also normal. Serial cardiac enzyme levels were normal, as were her liver and renal function tests. Her white cell count was $11 \times 10^9/L$ and her haemoglobin level was 144 g/L. Intermittent dizziness persisted after her admission. She was given zopiclone and mirtazapine at

night, while the duloxetine was skipped.

On day 5 of her admission, the patient had a generalised tonic-clonic seizure for 3 minutes with persistent uprolling eyeballs and was unresponsive for 5 minutes. She regained consciousness but remained drowsy thereafter. Later that day she developed a second episode of uprolling eyeballs and was given a 5 mg injection of diazepam. She then went into respiratory arrest and was given flumazenil to reverse a suspected benzodiazepine effect. She then went into cardiac arrest and cardiopulmonary resuscitation, including intubation, was commenced. She was given 5 doses of flumazenil, 8 doses of adrenaline and 1 dose of atropine but 1 hour of resuscitation failed to revive her. She died on 13 December 07.

An autopsy performed by the coroner showed unusual pulmonary thrombotic arteriopathy associated with changes of pulmonary hypertension. There was no other significant cause of death.

Discussion

Classical histopathological descriptions of pulmonary hypertension are similar to those found by the pathologist when he examined this patient post-mortem. Nonetheless, the only psychotropic medications implicated in the definitive development of pulmonary hypertension and/or thrombosis, are appetite suppressants such as fenfluramine. Other psychoactive substances like amphetamines or cocaine may also contribute to pulmonary hypertension. Despite this, the association between maternal use of SSRI (or SNRI) late in the third trimester and the risk of PPHN in the infant makes us more suspicious of this remote possibility.¹⁵

Having said that, there is still a theoretical possibility that the antidepressants used to manage our patient were the hidden culprits in her pulmonary hypertension. The reason for this is that one of the mediators in the pathogenesis of pulmonary hypertension is 5-hydroxytryptamine (serotonin). The 2 antidepressants prescribed to our patient may have had a synergistic effect, enhancing the serotonin level at synapses by both antagonism and reuptake inhibition. If serotonin reaches an exceptionally high level, it may be a cause of pulmonary hypertension, though this is just speculation.

Did our patient suffer from serotonin syndrome and was it related to her pulmonary hypertension? Probably no one can answer this question. Serotonin syndrome symptoms may include mental status changes (e.g. agitation, irritability, altered consciousness, confusion, hallucination, coma), autonomic instability (e.g. tachycardia, hyperthermia, diaphoresis, shivering, blood pressure lability, mydriasis), neuromuscular aberrations (e.g. hyperreflexia, incoordination, myoclonus, tremor, rigidity, ataxia), and gastrointestinal symptoms (e.g. abdominal cramping, nausea, vomiting, diarrhoea). Our patient did have a few of these symptoms but not the major or 'cardinal' ones of serotonin syndrome. Her complaints about irritability and fearfulness were quite non-specific and while palpitations

can be a sign of serotonin syndrome, it constitutes only an autonomic entity. Clinicians who suspect serotonin syndrome or who wish to determine the underlying cause of palpitations should arrange an electrocardiogram and physical examination.

What should we do when managing our patients with concomitant antidepressants? Of course we have to take care with drug dosages, paying special attention to the potential risk of drug-drug interactions. Clinicians must also consider the patient's physical condition, for example, liver and renal functions, and use drug combinations only when these are strongly indicated. In other words, we have to balance the risks and benefits of doing so. A substance abuse history should also be explored, paying attention to drug use such as cocaine, 'ice' or dieting drugs. The likelihood of serotonin syndrome, as mentioned above, should always be borne in mind, especially if both drugs may enhance serotonin activity. Clinicians must always be alert to possible signs and symptoms of serotonin syndrome or even pulmonary hypertension. This requires that the psychiatrist concerned takes a meticulous history and performs a comprehensive physical examination.

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