Case Report

Acute hypertriglyceridemia and hyperglycemia related to mirtazapine: A case report

Ebru Sahan[1], Aise Tangilntiz[2]
[1]Department of Psychiatry, Marmara University, Pendik Training and Research Hospital, Pendik, Istanbul, Turkey
[2]Department of Psychiatry, Bezmialem Foundation University Medical Faculty, Adnan Menderes Boulevard (Vatan Road), Fatih, Istanbul, Turkey

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ABSTRACT

A 42-year-old woman was hospitalized with depression and was started on mirtazapine 15 mg/day. Just one week after starting mirtazapine, severe hypertriglyceridemia and hyperglycemia were detected. Although these metabolic adverse effects have been reported before, to our knowledge this is the first case of hypertriglyceridemia and hyperglycemia occurring so early (just one week) after initiation of mirtazapine. The patient's glucose and triglyceride normalized nine days after discontinuation of mirtazapine. This case emphasizes the importance of regular glucose and triglyceride measurements at baseline and then regular monitoring in patients receiving mirtazapine treatment.

KEY WORDS: adverse effects, depression, hyperglycemia, hypertriglyceridemia, mirtazapine

INTRODUCTION

Two important neurotransmitters involved in the pathophysiology of depression are serotonin and noradrenaline[1]. Mirtazapine is an antidepressant from the piperazineazepine group, mainly used in the treatment of depression, which increases noradrenaline release by blocking alpha-2 autoreceptors[2]. This increase in noradrenaline levels facilitates cell firing by stimulating alpha-1 adrenoreceptors in the serotonergic cell body, which stimulates the release of 5-hydroxytryptamine (5-HT) in the synapses[3]. Increased serotonin in the synaptic space leads to increased transmission over 5-HT1 receptors, which is probably related to antidepressant and anxiolytic effects. In addition, mirtazapine blocks 5-HT2 and 5-HT3 receptors and acts as a 5-HT1A receptor agonist[4]. Mirtazapine has very weak muscarinic anticholinergic and histamine antagonist properties[5]. Common side effects associated with mirtazapine are somnolence (54%), dizziness (7%), increased appetite (17%), weight gain (8%), increased nonfasting serum cholesterol (15%) and increased serum triglyceride (6%) levels, elevated liver transaminases (52%), constipation (13%) and dry mouth (25%). Less commonly reported side effects (<1%) include activation of mania/hypomania, asthenia, agranulocytosis and neutropenia[6].

The European Atherosclerosis Society/ European Federation of Clinical Chemistry and Laboratory Medicine considers non-fasting triglyceride (TG) levels of >175 mg/dL and fasting TG levels of >150 mg/dL as upper limits while levels between 180-880 mg/dL, and above >880 mg/dL are considered mild to moderate and severe hypertriglyceridemia, respectively[7]. Fasting TG levels above 150 mg/dL can be considered as elevated TG levels, which is associated with an increased risk of atherosclerosis and cardiovascular diseases. Once TG levels increase above 500 mg/dL, and particularly above 1000 mg/dL, the most important clinical outcome is markedly increased risk of pancreatitis[8]. Here, we present a case with an elevation of TG levels three times the baseline level and elevation of glucose levels two times the baseline level, the elevation occurring within the first week of mirtazapine use.

Address correspondence to:
Dr. Ebru Sahan, Department of Psychiatry, Marmara University, Pendik Training and Research Hospital, Fevzi Cakmak Mah. Muhsin Yazicioglu Cad. No:10, Pendik, postal code: 34899, Istanbul, Turkey. Tel: +90 2166254545; E-mail: ebrushaan@hotmail.com

CASE REPORT

A 42-year-old Caucasian, married, housewife patient presented with a long-standing history of depression since the age of 25. Her history was notable for several visits to various psychiatric outpatient clinics over the course of eleven years due to anxiety, loss of motivation, feeling upset, hopelessness, pessimism, difficulty sleeping and "feeling sleepy all day''. She had a headache starting at the age of 20 but she was examined 5 years later by a neurologist and was started on amitriptyline, which she used for six months. The patient did not complain of the headache until the age of 31 years. Upon resumption of the depressed mood, anhedonia, early insomnia, feeling tired and being tearful all the time, she reported to the psychiatry outpatient clinic of another hospital. Although she continued her outpatient treatment, due to continuing complaints, she had been hospitalized three times and discharged with partial remissions until the age of 36 years. Despite taking several different medications including escitalopram, duloxetine, lamotrigine, sertraline, gabapentin, trazodone, venlafaxine, aripiprazole and lithium in various periods, the patient had never completely recovered. Due to the failure of symptom control in the outpatient setting, she was admitted to our hospital as an inpatient, which was overall her fourth admission. She was using metformin 1000 mg/day for her diabetes mellitus and nebivolol 5 mg/day for her hypertension. Her family history revealed major depressive disorder in her mother. She was a smoker, but she had never used alcohol or any other substance. The patient appeared to be overweight (weight: 72 kg, height: 160 cm, BMI:28.1). Her vital signs were as follows: blood pressure: 137/63 mmHg, heart rate: 105 beats/min and body temperature: 36.7 °C. Physical and neurological examinations were negative for any significant findings.

In the psychiatric examination, her mood was depressed and her affect was congruent with her mood. Her appetite was normal but she had early and middle insomnia. Based on these findings, she was diagnosed with depression. Her Hamilton depression rating scale score was 18 and Beck depression inventory score was 26. On the first day of hospitalization, a complete blood count, metabolic panel, hepatic and renal function tests and urine analysis were performed, which revealed the following abnormalities: A TG value of 572 mg/dL (normal: 50-150 mg/dL), fasting glucose level of 233 mg/dL (normal: 70-105 mg/dL), hemoglobin of 7.82 g/dL (normal: 12.2-16.2 g/dL). Her electrocardiogram showed sinus rhythm. HbA1c level was 5.1. Since she had impulse control problems, anxiety, early and middle insomnia, sertraline 50 mg/day, risperidone 1 mg/day and mirtazapine 15 mg/day were prescribed for her. Intravenous ferric carboxymaltose was administered for her anemia. On the seventh day of mirtazapine treatment, control blood tests revealed more than three-times increase in serum TG level (from 572 to 1637 mg/dL) and about two-times increase in serum fasting glucose level (from 233 to 432 mg/dL) for which fenofibrate 267 mg/day for

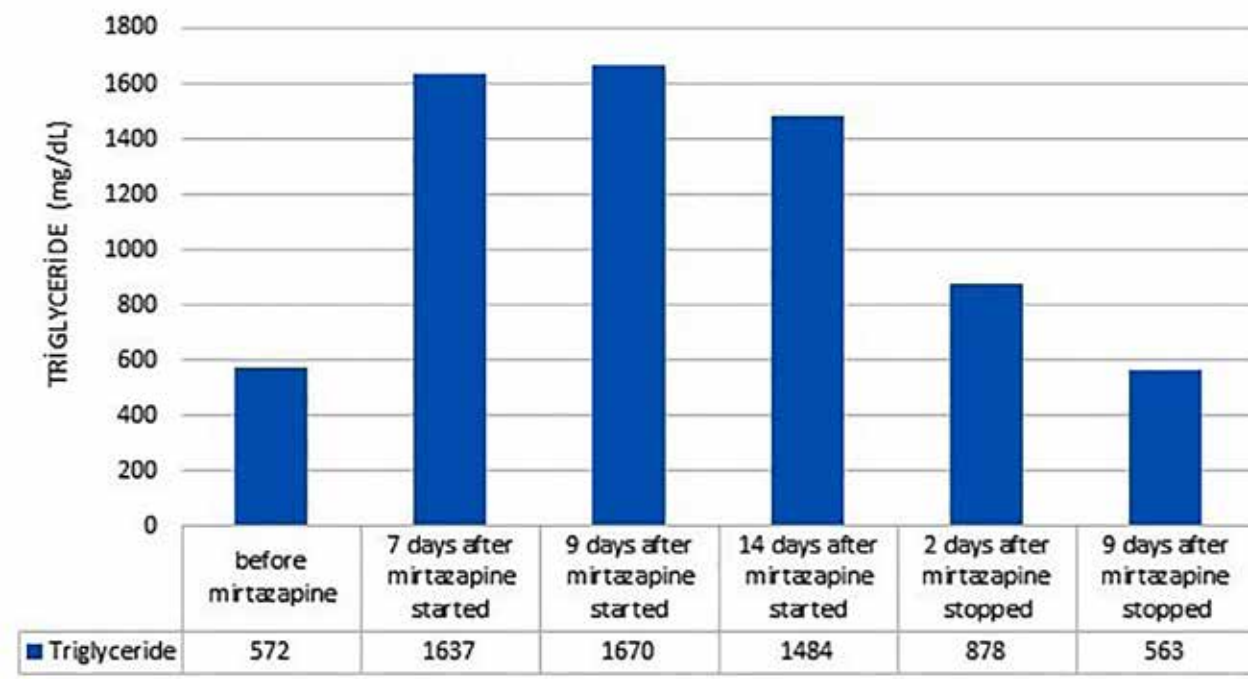

Fig 1: Serum fasting triglyceride levels before and after the initiation of mirtazapine.

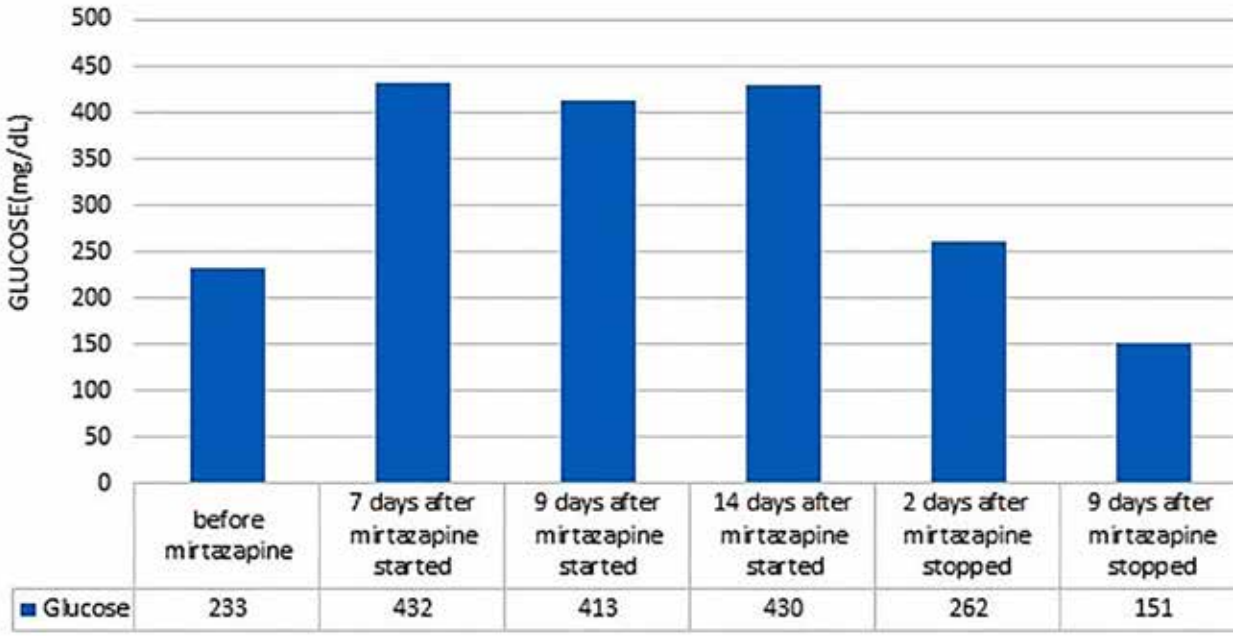

Fig 2: Serum fasting glucose levels before and after the initiation of mirtazapine.

hypertriglyceridemia and pioglitazone 30mg/day for hyperglycemia were started. Amylase and lipase were within normal limits. After two days, TG and glucose levels were still high (TG: 1670 mg/dl and glucose: 413 mg/dl). Mean capillary glucose measurements were 315 mg/dl for fasting and 330 mg/dl for nonfasting. Her impulse control disorder was in remission, therefore risperidone treatment was stopped. On the 14th day of admission, her weight was 0.7 kg less than her initial weight. The urine analysis was negative for ketones or protein. Her persistently elevated TG and glucose levels were suspected to be secondary to mirtazapine treatment, and therefore mirtazapine was stopped. Instead, the patient was started on trazodone for insomnia. Two days later, serum TG level dropped to 878 mg/dL and serum glucose level dropped to 262 mg/dL. Her psychiatric symptoms showed remarkable improvement and she was eventually discharged from the hospital. During her follow-up examination one week later, depressive symptoms were still in remission while her TG level was back to her baseline at admission (563 mg/dL on follow-up, 572 mg/dL on admission) and her serum glucose level had dropped to 151 mg/dL.

Figures 1 and 2 demonstrate the change in TG and glucose levels in chronological order, respectively.

DISCUSSION

The risk factors for hypertriglyceridemia include genetics, lifestyle and diet (*e.g.*, obesity, alcohol consumption and reduced physical activity), diseases and disorders (*e.g.*, metabolic syndrome, insulin resistance, diabetes mellitus, renal disease), and medications (*e.g.*, corticosteroids, estrogens, beta-blockers, thiazides, bile acid sequestrants and immunosuppressive agents)[8].

Various antidepressants like amitriptyline, clomipramine, fluoxetine, venlafaxine and citalopram have been associated with hypertriglyceridemia and/or acute pancreatitis[9-15]. In placebo controlled studies of the United States, nonfasting triglyceride increases to ≥500 mg/dL were observed in 6% of patients treated with mirtazapine, compared to 3% for placebo and 3% for amitriptyline[6]. However, few cases have been reported about elevated serum triglyceride levels above 1000 mg/dL associated with mirtazapine in the literature. Bowers *et al* described a patient with hypertriglyceridemia induced pancreatitis for whom the suspected cause of dangerously elevated TG levels was mirtazapine[16]. Chen *et al* reported a 44-year-old woman with acute pancreatitis and diabetic ketoacidosis due to hypertriglyceridemia which started two months after mirtazapine treatment[17]. Similarly, Duncan *et al* reported a 75-year-old male patient who developed hypertriglyceridemia followed by hyperglycemia two months after starting to use mirtazapine[18].

Our patient had concomitant diabetes mellitus and hypertriglyceridemia, which might have put her in a more vulnerable position for mirtazapine-induced hypertriglyceridemia and hyperglycemia, although she did not gain weight and was not in diabetic ketoacidosis.

Literature was more plentiful about mirtazapine

Table 1: ADR probability scale

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

related pancreatitis cases, suggesting the elevated serum triglyceride levels as its possible explanation. In addition to Chen *et al* and Bowers *et al*, Navarro *et al*, Sommer *et al*, Hussain and Burke, Lankisch and Werner, and Stone and Puri reported acute pancreatitis cases secondary to hypertriglyceridemia in patients using mirtazapine[19-24]. However, our patient did not have the symptoms, signs or laboratory evidence of pancreatitis.

A research study observed significantly impaired glucose tolerance in acutely depressed patients compared to healthy controls. Although glucose tolerance improved under mirtazapine treatment, insulin sensitivity was still impaired and remained significantly lower in patients compared to controls[25].

Concerning 'mirtazapine' and 'hyperglycemia', Fisfalen described a patient who was on mirtazapine for appetite stimulation and who had severe hyperglycemia in addition to a 16-kg weight gain[26]. Chen *et al* reported hyperglycemia secondary to mirtazapine therapy in a 37-year-old man[27].

This patient had well-controlled diabetes before mirtazapine usage so we did not detect any diabetes complications. The antidiabetic drug metformin has not been related to hypertriglyceridemia, though it ameliorates obesity-associated hypertriglyceridemia in mice[28]. The antihypertensive drug nebivolol, which our patient was using, has not been shown to cause significant changes in insulin sensitivity and TG levels[29,30].

The Naranjo scale, shown in Table 1, evaluates the likelihood that an adverse effect is caused by a pharmacologic agent[31]. The Naranjo scoring system has been validated and is used in clinical practice. The probability that the adverse event was related to drug therapy was classified as Definite ≥ 9, Probable = 5-8, Possible = 1-4, Doubtful ≤ 0 that an adverse drug reaction was caused by a drug or some other factor.

A "definite" reaction was one that (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues; (2) followed a recognized response to the suspected drug; and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure. A "probable" reaction (1) followed a reasonable temporal sequence after a drug; (2) followed a recognized response to the suspected drug; (3) was confirmed by withdrawal but not by exposure to the drug; and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.

In our patient, TG and glucose levels were found to be elevated only within the first week of mirtazapine treatment and were back to baseline shortly after the cessation of mirtazapine.

There are previous conclusive reports on this reaction (+1), the suspected event has appeared after the offending agent was administered (+2), adverse drug reaction improved when the offending agent was discontinued (+1), there are no alternative causes that could solely have caused the adverse drug reaction (+2). Naranjo adverse reaction scale score was "6" which corresponds to "probable causality".

CONCLUSION

In conclusion, depending on the possible association of mirtazapine and hypertriglyceridemia, serum glucose and TG levels should be measured before and shortly after starting mirtazapine treatment to ensure patient safety, especially in patients who are at high risk.

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We have no conflicts of interest to disclose.

Authorship criteria: All authors contributed to (1) history taking, physical and psychiatric examination and treatment of the case; the acquisition of laboratory data and interpretation of side effects; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

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