Correspondence

Another dangerous combination for hypoglycemic coma: concurrent use of sibutramine and lorazepam

Sir,

With increasing demands to treat obesity in both medical and psychological aspects, many drugs are developed to lower human body weight. Those widely used anti-obesity drugs, such as olistat and sibutramine, are generally safe. But serious adverse effects could be developed when it is concurrently used with other medications. We report a patient who developed hypoglycemic coma due to concurrent use of sibutramine and lorazepam.

A 32-year-old woman presented to the emergency department because of disturbed consciousness and an episode of generalized seizure attack. On arrival, she was comatose with a blood pressure 108/58 mmHg, pulse rate 96 beat/min, respiration rate 20 breath/min and body temperature 35.6°C. The result of a focused neurologic examination was normal. A capillary blood glucose measurement was 27 mg/dl. She regained consciousness promptly after treated with bolus of 50% dextrose and continuous infusion of 10% dextrose. She had no history of systemic illness. She was treated with sibutramine 10 mg per day by another hospital due to over-weight. She developed insomnia, for which she used lorazepam 2 mg on as needed basis. Her families stated that she complied poorly with follow-up program and had no food intake for less than 12 h prior to admission. Her BMI was 22 at this presentation. The laboratory data including complete blood count, liver function tests and serum creatinine were normal. The serum ethanol level was zero, but she had a positive urinary test for benzodiazepine. An endocrinologist was consulted and she was admitted. At the ward, her serum glucose levels were checked every hour and no further hypoglycemic episode was noted. Her albumin and total protein were 3.8 and 6.5 g/dl, respectively. She had a insulin level of 5.2 μU/ml (normal range, 5–25 μU/ml), a negative urinary sulfonylurea screening test and a suppressible C-peptide suppression test. She had a normal serum cortisol level of 21.66 μg/dl at 8:00 a.m. and a normal human growth hormone of 0.1 ng/ml. Her thyroid function panel was also normal (triiodothyronine 89.26 ng/dl; thyroid-stimulating hormone 1.62 μU/ml; and free thyroxine 1.61 ng/dl). The magnetic resonance imaging of the abdomen showed no pancreatic mass. She was discharged on the 5th hospital day. On follow-up at clinic for 6 months, she no longer had hypoglycemic episode.

This young woman who used sibutramine and lorazepam concurrently developed hypoglycemic coma after less than 12 h of fasting. The promptly regained consciousness after bolus dextrose infusion argued against the depressed consciousness was caused by lorazepam in this patient. There was no attributable cause such as medication errors, ethanol ingestion, neoplasm or liver diseases. The cause of hypoglycemic coma in this patient could be multifactorial in origin involving lowered energy reservoir, failed glucose homeostasis (hypoglycemic unawareness and blunt counterregulatory responses) and a probable direct glucose lowering effect of sibutramine. Lack of repeated evaluation of the body weight, nutritional or psychological status contributed to sibutramine over-treatment in this patient. Prolonged fasting can contribute to hypoglycemia, but severe hypoglycemia (serum glucose < 50 mg/dl) almost never occurs within the first 48 h of fasting due to glucose homeostasis of the human body.1 Massive weight reduction can cause reduced glucose counterregulatory hormonal responses, increased insulin sensitivity and perturbed cognitive function.2 Sleep could impair or delay counterregulatory-hormone responses to hypoglycemia in normal human subjects and diabetic patients.3,4 However, lowering the plasma glucose to a nadir of 2.2 mmol/l (39.6 mg/dl) induces
a wake-up response in most healthy individuals during sleep.\textsuperscript{5} The use of alprazolam had been demonstrated to reduce the neuroendocrine response to insulin-induced hypoglycemia in human.\textsuperscript{6}

Sibutramine is a neuropharmacological drug with serotonin and noradrenaline re-uptake inhibitor (SNRI) property.\textsuperscript{7} It was subsequently found to have weight-losing effect.\textsuperscript{8} It has been also used in treating insulin resistance and polycystic ovary syndrome.\textsuperscript{9–11} The mechanisms of action are increasing satiety, stimulating thermogenesis, and increasing the efferent sympathetic activity to thermogenically active brown fat.\textsuperscript{12,13} Common side effects of sibutramine are insomnia, nausea, dry mouth, constipation and cardiovascular events.\textsuperscript{14} On reviewing medical literatures, we found no report regarding the association between hypoglycemia and sibutramine. Nevertheless, there are plenty of evidences suggesting that sibutramine can decrease insulin resistance and lower serum glucose profile in both obese individuals and diabetic patients.\textsuperscript{15–17} The metabolite of sibutramine can reduce serum glucose level, maintain insulin-mediated muscle glucose uptake and reduce hepatic gluconeogenesis.\textsuperscript{18} Antidepressants including serotonin selective re-uptake inhibitor (SSRI, fluoxetine) and SNRI (sertraline, nefazodone) had been reported with a glucose-lowering effect and associated with hypoglycemia.\textsuperscript{19–22} Whether sibutramine has such direct glucose-lowering property remains unanswered.

In conclusion, concurrent use of sibutramine and lorazepam could potentiate the development of severe hypoglycemia in a patient with low BMI. We suggest that any drugs with the potential of causing hypoglycemic unawareness or hypoglycemic effects should be used with caution in patients treated with sibutramine.

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References


A 33-year-old woman presented with a week’s history of progressive backache, weakness and dysphagia. The onset of her symptoms coincided with tapering of 4-week course of oral corticosteroids (prednisolone), which was instituted to treat a severe pneumonic illness requiring admission to intensive care and a short period of assisted ventilation. She did not have any previous history of obstructive Airways or interstitial pulmonary disease. Her respiratory illness was presumed to be due to viral pneumonia but no serological or microbiological evidence for infection was identified. She was diagnosed with Crohn’s disease since as a child, based on histology of her colonoscopic biopsy. The bowel disease was quiescent for many years and she was essentially asymptomatic for Crohn’s disease at presentation. She also suffered from asthma, which was well controlled on regular use of inhaled steroids and beta agonists.

On this occasion, she had developed progressive muscle weakness. She could not roll over in bed, lift her arms or rise. She also noted difficulty with swallowing both liquids and solids. Clinical examination at the Accident and Emergency department showed mild bifacial weakness, dysarthria and weak cough. She was tachypnoeic with a respiratory rate of 25 breaths per minute. Limb examination revealed globally flaccid tone and profound proximal weakness (MRC 1/5). Forced vital capacity was <1 l and arterial blood gas examination showed a PaO$_2$ on air of 8.9 kPa (11.10–14.4 kPa). She was transferred to the intensive care unit for intubation and assisted ventilation. The medical team suspected a diagnosis of acute inflammatory demyelinating polyneuropathy (Guillain–Barre syndrome).

On the following morning, when she was seen by us, she was still being ventilated but was off all sedation and muscle relaxants. She had no skin rash, keratosis or arthropathy. Examination revealed severe weakness in her neck flexors, bifacial and bulbar muscles and proximal limb muscles. Her eye movements and sensory examination were normal. The tendon reflexes were easily elicited and plantar responses were flexor. The persistence of tendon reflexes was considered to be incompatible with the severity of muscle weakness in a ventilated patient with presumed Guillain–Barre syndrome and a diagnosis of polymyositis was preferred. The clinical diagnosis of polymyositis was supported by marked elevation of her serum creatinine kinase (CK) of 3319 IU/l (normal <145) and ESR of 115 mm/h (normal <15). She was commenced on a course of intravenous methylprednisolone (1 g/day for 3 days), followed by oral prednisolone (1 mg/kg/day; total dose 80 mg daily) and alendronic acid (70 mg/week) for osteoprotection.

Subsequent investigations confirmed the clinical diagnosis of acute polymyositis. Electromyography (EMG) showed insertional activity, myopathic potentials characterized by short-duration, low-amplitude polyphasic units on voluntary activation, increased spontaneous activity with fibrillations, complex repetitive discharges and positive sharp waves, all of which were consistent with an inflammatory myopathy. There was no motor nerve conduction block, sensory studies were normal and repetitive motor nerve stimulation showed no evidence of neuromuscular junction dysfunction. Histological examination of a needle muscle biopsy taken from her left quadriceps muscle revealed evidence of lymphocytic infiltration and muscle fibre necrosis with no perifascicular muscle atrophy (Figure 1), appearances in keeping with her diagnosis of polymyositis. Cerebrospinal Fluid (CSF) biochemical and cytological examination was normal. Serum and CSF electrophoresis revealed paired oligoclonal bands, consistent with a systemic immune response. Serological screening was positive for anti-Jo-1 antibodies. An elevated serum troponin T of 1.01 g/l (less than 0.01) was found; however, electrocardiographic appearances were unremarkable apart from sinus tachycardia. Echocardiographic examination showed normal left ventricular function (Ejection Fraction >55%). Abdominal ultrasound examination showed mild fatty hepatic infiltration and normal renal anatomy.

She experienced a rapid clinical improvement with steroid treatment. She was successfully