

Case Report

What's Tramadol Got to Do with It? A Case Report of Rebound Hypoglycemia, a Reappraisal and Review of Potential Mechanisms

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Background: Tramadol has gained traction as an analgesic of choice among pain practicing physicians. However some concerns regarding a previously unlabeled adverse reaction – hypoglycemia – have cast it in a dim light. Prior reports have noted an associated risk of hospitalization for hypoglycemia after tramadol use, but whether tramadol is the main causal agent is poorly understood and the underlying mechanisms are not well delineated.

We present a unique case of rebound hypoglycemia as a variation of the theme of tramadol's adverse effect profile in a patient with type 1 diabetes mellitus, and reappraise potential mechanisms underlying this underappreciated phenomenon.

Case Presentation: A 71-year-old woman presented with right buttock pain and right lateral leg discomfort of 9-month duration. Her physical exam suggested sacroiliac joint (SIJ) etiology, confirmed by magnetic resonance imaging (MRI). She was scheduled for an SIJ-diagnostic and therapeutic block and started on tramadol 50 mg 3 times daily on as needed basis. The patient subsequently developed severe hypoglycemia initially resistant to euglycemia restorative interventions with a rebound episode. Hypoglycemia resolved with oral ingestion of high levels of glucose and the patient was taken off tramadol. Fortunately, she did not require hospitalization.

Discussion: The clinical scenario described is a case of rebound hypoglycemia after tramadol use in a patient with type-1 diabetes naïve to opioid analgesics. The episodes of hypoglycemia aligned perfectly with the anticipated pharmacodynamic and pharmacokinetic properties of tramadol. The specificity and temporality of events after tramadol use in this patient fulfilled causality criteria. Tramadol may cause rebound hypoglycemia in patients via interference of the intrinsic euglycemia-restoration pathways and a blunted autonomic counter-regulatory response to antecedent hypoglycemia. Its use must be tempered by this underappreciated adverse effect profile.

Key words: Tramadol, hypoglycemia, sacroiliac joint arthritis, type 1 diabetes mellitus, serotonin uptake inhibitors, glutamate receptor 4

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Tramadol hydrochloride, once considered a safe drug relative to existing options in the pain physician's analgesic armamentarium, has recently garnered some notoriety (1). Recent reports highlight a rare but potentially fatal side effect –

hypoglycemia – attributed to 2 mechanisms (2). Its inhibitory action on serotonin and norepinephrine reuptake, coupled with its enhancement of peripheral glucose utilization via the glutamate receptor 4 (GLUT4), can lead to a sharp drop in blood glucose

levels (3,4). In comparison to codeine, another opioid, tramadol was associated with a 3-fold increase in the risk of hospitalization for hypoglycemia within the first 30-days of incident use (1).

This hypoglycemic effect has been noted in those with and without diabetes but the heterogeneity of diabetes phenotypes raises interesting questions regarding the observed glucopenic effect of tramadol in the former as well as the mechanisms underlying the process (2). For patients on an insulin management regimen, prior studies show that those with type-1 diabetes report a 2-fold increased risk of hypoglycemia compared to those with type-2 diabetes (5). The differential baseline risk is in part due to the underlying pathophysiology – the former are intrinsically insulin deficient, the latter insulin resistant (6). This difference warrants delineation of whether tramadol-induced hypoglycemia varies between the 2 major groups.

We present a case of rebound hypoglycemia in a patient with type-1 diabetes, who becomes precipitously hypoglycemic within 10 – 12 hours after ingestion of tramadol. The rapid time to induction of hypoglycemia contrasts with prior reports and highlights potential mechanistic differences in the glucopenic effect of tramadol heretofore unreported between individuals with type-1 vs. type-2 diabetes. To our knowledge and per our review of the current literature, there are no reports of tramadol-induced rebound hypoglycemia in a patient with type-1 diabetes. We briefly review the counter regulatory responses to hypoglycemia under both diabetic conditions and how these may be disparately affected by tramadol.

CASE PRESENTATION

A very active 71-year-old woman presented to the pain clinic with a complaint of right buttock pain and right lateral leg discomfort. The pain onset occurred 9-months ago during a bird watching trip to Costa Rica when she noticed right buttock pain with prolonged walking, standing, or sitting. She described the pain as stabbing in quality, with radiation to her right knee and right hip. The pain was persistent, moderate in severity, rated at 6/10 by visual analog score, and aggravated by changes in posture. Associated symptoms included joint stiffness, paresthesia, and right leg pain. Pertinent negatives included no abdominal pain, bladder or bowel incontinence, dysuria, fever, neck or back pain, headaches, hemiparesis, pelvic pain, perianal numbness, tingling, loss of appetite, and unintentional weight loss or weight gain. She was referred to the pain clinic by

her primary care physician after several months trial of physical and aqua-therapy, home exercises, bed rest, heat, walking, and non-steroidal anti-inflammatory drugs (NSAIDs) failed to provide any therapeutic relief.

Other than taking an antihypertensive and novolog (5 units prandial) and glargine (10 units nightly) for type-1 diabetes, she did not have any other comorbidity. She has been on insulin for 36 years with no prior episodes of severe hypoglycemia requiring hospitalization.

Investigations

Her physical exam was only remarkable for positive right lumbosacral neural tension and a positive Fortin's finger sign test on the right sacroiliac joint (SIJ) and gluteal area. She had normal lumbar lordosis, symmetric hip heights, no paraspinal tenderness, and a negative straight-leg raise test. Studies with magnetic resonance imaging (MRI) revealed multilevel lumbar degeneration with severe canal stenosis at L3-L5 and foraminal stenosis at L2-4.

Differential Diagnosis

At this point, the differential diagnosis considered included right SIJ dysfunction, right sciatic nerve compression, osteoarthritis of the lumbar spine with radiculopathy, and neurogenic claudication. The patient was naïve to opioid analgesics so was started on tramadol 50 mg 3 times daily pro re nata and scheduled for a right sacroiliac joint diagnostic and therapeutic block.

Time Course

She reported taking the first dose of tramadol (Ultram ER) at 10:00 am prior to breakfast the next morning (Fig. 1). She had symptomatic pain relief until around 6:00 pm, when she took a second dose (Fig. 1). She reports keeping to her usual daily and mealtime routine. Her pre-dinner glucose level at this time was 93 mg/dL. At 7:10 pm her postprandial glucose level was 70 mg/dL. She ate a cookie to boost her levels but 3 hours later was hypoglycemic with glucose of 51 mg/dL at 10:30 pm. She then ate a peanut butter and jelly sandwich and drank glass of milk to stabilize her levels. At 1:15 am, her glucose had dropped to 42 mg/dL. She reported fatigue and diaphoresis so drank 2 full cups of orange juice (equivalent of 480 mL of juice containing 48 g of sugar). At 1:45 am, she was still hypoglycemic at 56 mg/dL. She then drank 4 more full cups of orange juice. By 3:08 am, her levels had reached 80 mg/dL. With no change by 3:45 am, she was less symptomatic

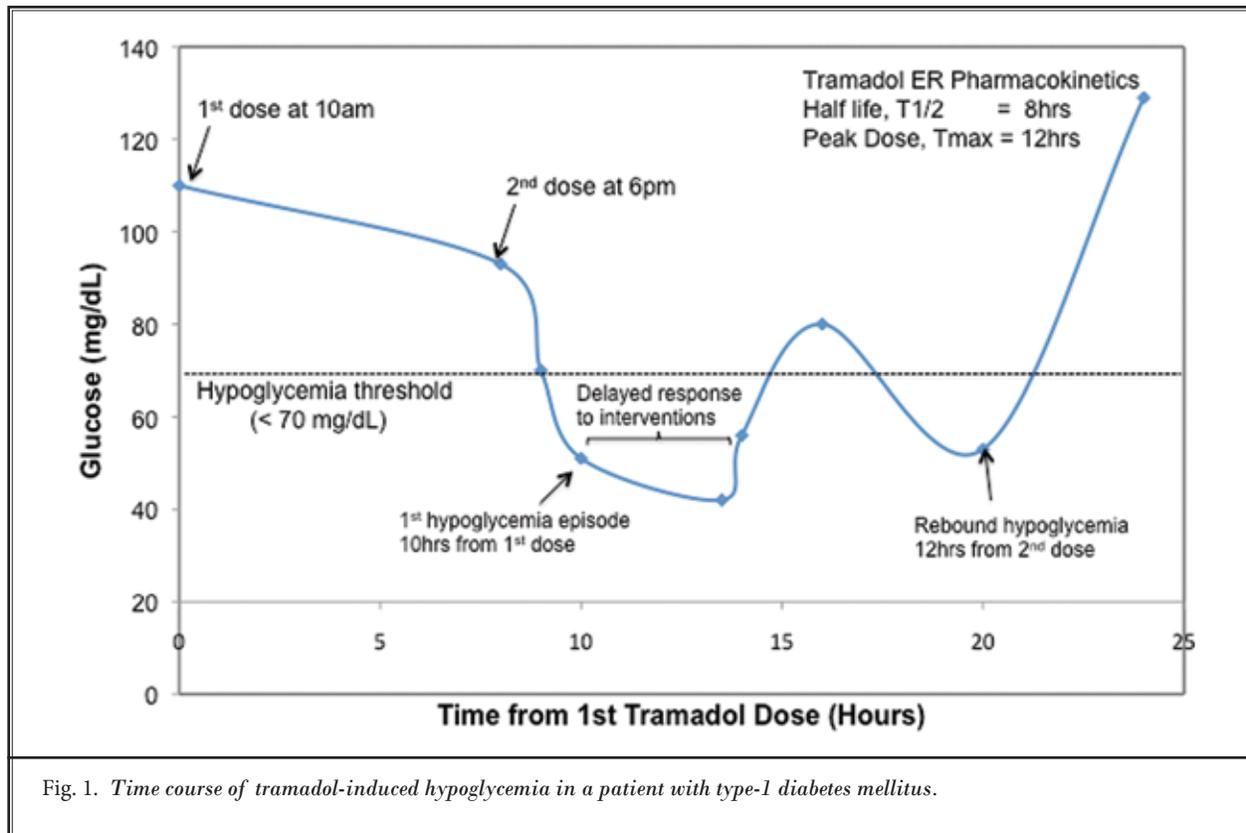


Fig. 1. Time course of tramadol-induced hypoglycemia in a patient with type-1 diabetes mellitus.

so went to sleep. She woke up at 7:30 am with diaphoresis and chills, hypoglycemic with glucose of 53 mg/dL. She skipped her morning insulin and having run out of orange juice, drank some milk, and ate some cereal and fruits. Four hours later, her hypoglycemia resolved.

The patient reported to clinic the next day, was taken off tramadol, and underwent a right sacroiliac joint diagnostic and therapeutic block, with 100% pain relief. A week after being off tramadol, the patient remained euglycemic and asymptomatic

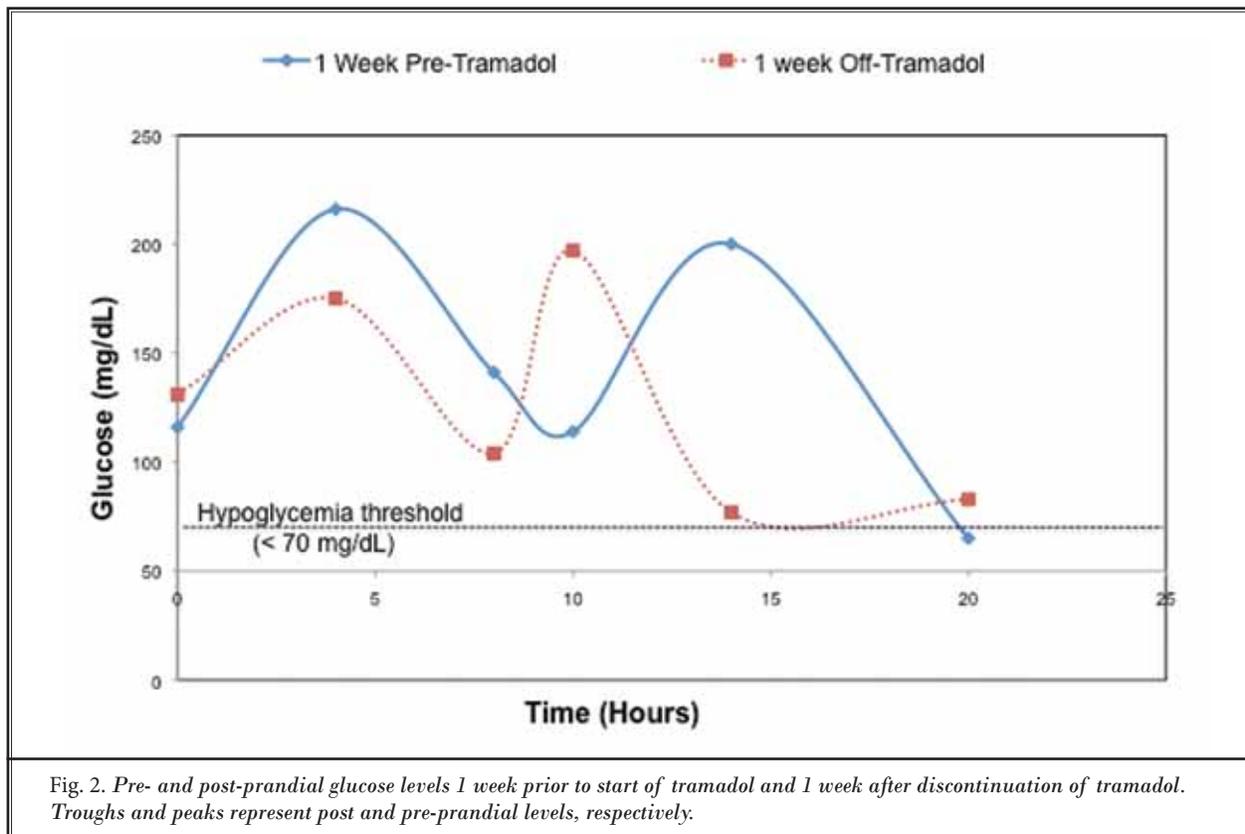
Discussion

The recent trend of tramadol-induced hypoglycemia suggests the use of this analgesic for pain management should be done with careful consideration of its potential complications (7-9). This case adds to the growing literature but also uniquely highlights previously undocumented rebound hypoglycemia after tramadol use in a patient with type-1 diabetes. While the exact mechanism is not fully understood, it appears that a rebound effect may occur via: 1) tramadol initiated interference of the intrinsic pathways to restore eugly-

cemia, and 2) a blunted autonomic counter-regulatory response to antecedent hypoglycemia.

Several reports have delineated strong associations between tramadol use and hospitalization but do not provide adequate evidence of causation (1,2). By successfully implementing hypoglycemia management interventions at home, our patient avoided hospitalization. From this perspective, she may appear to buck the trend of hospitalizations for hypoglycemia after tramadol use (7,8). Nonetheless her experience of hypoglycemic symptoms after tramadol use is consistent with prior reports and satisfies Hill's criteria for causality: consistency (same findings have been reported by others), specificity (effect is observed in a specific population with a specific condition), temporality (effect occurs after the cause and in the expected time frame), and biological gradient (the presence of the factor can trigger the event) (10,11).

Review of the timeline of events as documented by the patient implicates tramadol as the precipitant of her hypoglycemia. As someone who had lived with her condition for 36 years, she was adept at managing



episodes of hypoglycemia. According to her report, this was the first time she experienced severe hypoglycemia with significant delayed response to glycemic interventions. This was confirmed in a review of her baseline glucose levels where we compared her pre- and post-prandial glucose levels one week before tramadol was started and discontinued, respectively (Figs. 1 and 2). In general, her levels were above the hypoglycemia threshold (Fig. 2). This observation and the fact that she was opioid naïve and only experienced severe hypoglycemia after index exposure to tramadol, lends support to tramadol as the main culprit.

The pharmacokinetic profile of tramadol shows it has a half-life of 7.9 hours (for Ultram ER) with the maximum serum concentration, C-max of 208 ng/mL, the time to attain this peak concentration, T-max of 12 hours, and bioavailability of 85% – 90% (12,13). The first and second episodes of hypoglycemia occurred approximately 10 and 12 hours, respectively, from each episode of tramadol ingestion, when one expects maximum serum concentrations (Fig. 1) and peak effect of the drug. As noted elsewhere, a plausible mechanism

for tramadol-induced hypoglycemia relates to its pharmacodynamic properties (13,14). Tramadol activates the mu opioid receptor but blocks central serotonin and norepinephrine reuptake (1). Serotonergic pathways are known to modulate peripheral glucose utilization whereas activation of mu opioid receptors modulates insulin signaling and sensitivity (3). Tramadol is thought to exert its hypoglycemic effects via these pathways by reducing hepatic gluconeogenesis and increasing peripheral utilization of glucose (4).

In patients without diabetes, the first line of defense to hypoglycemia is release of fast-acting glucagon for global control of gluconeogenesis (5). Insulin production is suppressed and subsequently epinephrine, norepinephrine, and cortisol aid in glycogenolysis and lypolysis of fatty acids to restore euglycemia (5). Due to the atrophy of pancreatic cells, glucagon release is lost in patients with type-1 diabetes (6). Compared to individuals without diabetes, there is less of a robust response in type-1 diabetics as epinephrine serves as the key defense against hypoglycemia (5). By contrast, the response in type-2 diabetes depends on the degree of

progressive beta cell failure and insulin resistance. Response to hypoglycemia may therefore vary based on the diabetic phenotype, the underlying pancreatic pathology, and the consequent hormonal vs. regulatory mechanism. Tramadol, which indirectly increases serotonin levels, may interfere centrally with the counter regulatory response to hypoglycemia (4,5).

Ironically, antecedent hypoglycemia blunts the response of tissues to circulating epinephrine in type-1 diabetes and results in further decreased autonomic regulation of hypoglycemia (5). This may explain the delayed response to interventions to restore euglycemia by our patient, eventually resulting in rebound hypoglycemia (Fig. 1).

The absence of glucagon and the increased sensitivity to disruptions in counter-regulatory hormones may explain why individuals with type-1 diabetes may be generally more susceptible to tramadol-induced hypoglycemia. Other factors such as age, gender, comorbidity, genetic polymorphism, and use of glucopenic medications may also influence risk of hypoglycemia (1,4,5). Physicians prescribing tramadol for pain management should consider these risks in their decision to use this medication.

Our case underscores unique challenges of medical management of chronic pain and the importance close monitoring of patients on opioid analgesics (15). Tramadol-induced rebound hypoglycemia may be a significant but underappreciated phenomenon. Our

observation warrants more serial reports and future studies to ascertain whether its occurrence is unique to individuals with type-1 diabetes or is a more generalized but underreported event. Management of tramadol-induced hypoglycemia should be tailored to the specific needs of the individual but generally involve administering oral glucose, intramuscular glucagon, intravenous dextrose (for severe cases), withdrawal of tramadol and other hypoglycemic agents, and close monitoring of blood glucose levels until euglycemia is attained (1,2,7).

CONCLUSION

The use of tramadol for pain control must be tempered by its potential adverse effects profile (1,5,9). Pain management experts who often prescribe this medication would do well to educate their patients about these complications and to provide them with treatment strategies. For populations such as those with diabetes, we caution vigilance for potentially fatal outcomes and to consider alternatives with equivalent benefit and less harm.

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