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Impact of weight loss surgery on valproic acid levels: A case report

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Abstract

Weight loss surgery has become more common in the United States because of the increasing rates of obesity. The physiological changes caused by weight loss surgery have the potential for clinically significant changes in the pharmacokinetic parameters of mood stabilizers, including valproic acid (VPA). A patient with a history of Roux-en-Y gastric bypass and bipolar disorder was hospitalized because of mania. The dosing regimen of the VPA was changed multiple times due to unexpectedly low and inconsistent trough levels. Despite a significant increase in the total daily dose, the final trough level obtained was not significantly different than the initial level. The VPA was changed from the delayed-release to the immediate-release formulation to achieve better absorption. However, no trough level was obtained after this change. Weight loss surgeries, such as Roux-en-Y gastric bypass, may continue to impact the pharmacokinetic parameters of VPA for several years after the procedure. This patient was titrated to a dose of 39 mg/kg/day (typical range 20-30 mg/kg/day) with minimal change in level. Pharmacokinetic changes are a concern in the use of mood stabilizers, including VPA, after weight loss surgery. Close monitoring is essential for safe and effective treatment. If strict drug level monitoring is not an option, it may be preferable to consider an alternative mood-stabilizing treatment. Switching to the immediate-release formulation of VPA may also be an option; however, further investigation is required to determine if this makes a clinical difference in the management of bipolar disorder.

Keywords: weight loss surgery, Roux-en-Y, valproic acid, divalproex

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Introduction

Adults in the United States continue to have the highest prevalence of obesity in the developed world, with an estimated rate of 38.9%, according to a 2013 to 2016 National Health and Nutrition Examination Survey dataset.[1] Weight loss surgery (WLS) is among the most prevalent elective general surgeries in the US, with approximately 205 000 surgeries performed in 2018.[2]

Around two-thirds of patients undergoing WLS have a history of a psychiatric disorder, and it is estimated that 23% of WLS patients have a mood disorder.[3,4] The body undergoes many physical and anatomical changes after WLS, which can influence medication safety and efficacy. Many pharmacokinetic (PK) parameters are impacted by WLS, from increased stomach pH to faster gastric emptying and gastrointestinal (GI) transit time.[5,6] These PK changes can further complicate how some oral medications are absorbed based on parameters like drug disintegration, dissolution, and solubility, which are all altered through WLS.[6,7] These parameters can also vary based on the type of WLS.

Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), gastric banding (GB), and biliopancreatic diversion with duodenal switch are common types of weight loss procedures endorsed by the American Society for Metabolic and Bariatric Surgery.[1] SG is one of the most common, with 63% of procedures performed compared with RYGB at 30% and GB at 2%, according to a 2012 to 2015 study.[1,8] WLS can be further classified into restrictive and malabsorptive types. The restrictive type limits the physical volume of food that can be taken in, and the malabsorptive type impacts the absorption of food through the diversion of parts of the GI tract. RYGB is considered both a restrictive and malabsorptive procedure as a smaller part of the stomach gets directly attached to the small intestine, bypassing the rest of the stomach and the initial segment of the small intestine. SG and GB are mainly restrictive procedures. Most of the stomach is removed with a sleeve-like pouch remaining in SG, and a band is placed on the upper part of the stomach to physically restrict intake in GB.[7]

Previous literature has described the impact WLS has on antidepressants, which is the most common class of medication used by patients undergoing WLS.[9] However, there is a paucity of evidence to describe the impact of WLS on mood stabilizers. Approximately 70% of patients with bipolar disorder who are taking psychotropic medications are either overweight or obese.[10-12] WLS is a proven treatment that is effective in reducing obesity-related comorbidities.[1] Owing to the increasing number of WLS being performed each year, it is crucial to better understand how WLS can impact patients' medications postoperatively. Maintaining therapeutic drug levels after WLS is important in many conditions. Patients with bipolar disorder should be monitored closely because of the significant suicide risk and the potential for more frequent hospitalizations associated with acute mood symptoms.[13,14]

One mood stabilizer commonly used in bipolar disorder treatment that requires therapeutic drug monitoring is valproic acid (VPA) and its derivative, divalproex sodium. There are 2 different VPA dosing strategies in patients experiencing a manic episode. A fixed-dosing regimen typically starts at 500 to 750 mg/d. The dose can be increased by 250 to 500 mg/d every 1 to 3 days, depending on clinical response, adverse effects, and serum concentrations.[15] VPA can be given as a weight-based loading dose for more rapid symptom control. The recommended starting dose is 20 to 30 mg/kg/day. Steady state is usually achieved after 3 to 5 days, at which point the dose can be increased or decreased by 250 to 500 mg/day based on clinical response and VPA levels.[16,17] The maximum recommended dose is 60 mg/kg/day; however, many patients can achieve a stable therapeutic VPA level at 20 mg/kg/day.[18] We present a case of a patient with bipolar disorder treated with VPA who experienced lower-than-expected drug levels despite receiving higher doses 9 years after WLS.

TABLE 1: Medications before admission

Medication and Dose	Indication
Atomoxetine 100 mg once daily	ADHD
Bupropion IR 100 mg 3 times daily	Mood disorder
Clonidine 0.1 mg twice daily	ADHD
Amphetamine/dextroamphetamine 20 mg 3 times daily	ADHD
Divalproex DR 1250 mg twice daily	Bipolar I disorder
Fluticasone nasal spray 50 mcg once daily	Allergic rhinitis
Lisinopril 40 mg once daily	Hypertension
Metoprolol succinate 50 mg once daily	Hypertension
Quetiapine IR 350 mg nightly	Bipolar I disorder

ADHD = attention-deficit/hyperactivity disorder; DR = delayed release; IR = immediate release.

Case Report

A 48-year-old male presented to the emergency department (ED) with paranoid ideation. His past psychiatric history included bipolar I disorder, posttraumatic stress disorder, attention-deficit/hyperactivity disorder, and several substance use disorders, including cocaine, methamphetamine, and nicotine. His relevant medical conditions included gastroesophageal reflux disease, a history of GI bleed, type II diabetes mellitus, and hypertension. The patient had a history of class III obesity (body mass index [BMI] > 40 kg/m^2) and had received a RYGB surgery 9 years before the relevant admission. At the time of presentation to the ED, the patient weighed 89 kg and had a BMI of 27 kg/m^2 (overweight). Immediately before admission, the patient was being treated with atomoxetine, bupropion immediate release (IR), clonidine, amphetamine/dextroamphetamine, divalproex delayed release (DR), and quetiapine IR (see Table 1). Of note, the patient had been treated with the extended-release (ER) formulation (2000 mg/d) of divalproex sodium for at least 1 year, and the formulation had been changed to a total daily dose (TDD) of 2500 mg (1250 mg twice daily) of the DR formulation approximately 1 month before admission due to worsening symptoms. In the ED, the patient tested positive for amphetamines on a urine toxicology panel, likely due to the use of his prescribed amphetamine/dextroamphetamine. The patient did report the use of methamphetamine and ketamine approximately 1 month before admission. Labs were grossly within normal limits with the exception of elevated potassium of 5.8 mmol/L (3.3-5.3 mmol/L), elevated blood urea nitrogen of 30 mg/dL (6-20 mg/dL), and a low albumin of 3.3 g/dL (3.6-4.9 g/dL). On the evening of day 1, the patient had a VPA level of 61.2 µg/mL (50-125 µg/mL). Although the timing of the most recent dose before ED admission could not be definitively determined, the patient and residential facility staff report indicated that he was

TABLE 2: Divalproex and valproic acid doses and trough levels during admission

		Divalproex/Valproic Acid Dosing Regimens Throughout Hospitalization				
	1250 DR Twice Daily (Before Admission)	1250 DR mg Nightly	1250 mg DR Twice Daily (Home Dose)	1500 mg DR Twice Daily	1500 mg DR in the Morning, 2000 mg DR Nightly	1000 mg VPA IR Syrup Twice Daily
Total daily dose (mg/kg/day)	28	14	28	34	39	22
Corresponding VPA level (μg/mL)	61.2	N/A	N/A	46	63	N/A

DR = delayed release; IR = immediate-release; VPA = valproic acid.

adherent to all medications except for bupropion and had received his morning dose of divalproex DR before admission. Therefore, this level was likely close to a trough level.

In the ED, the patient displayed symptoms of mania, including restlessness, rapid speech, and a circumstantial thought process. Clonidine was continued at the same doses the patient was prescribed before admission. The dose of divalproex DR was originally resumed at 1250 mg nightly because of confusion surrounding the home dose. The dose of quetiapine was initially increased from 350 to 500 mg nightly because of the severity of symptoms. Bupropion and amphetamine/dextroamphetamine were held because of the possibility that they may exacerbate the mania and anxiety symptoms. Atomoxetine was held because of the perceived lack of efficacy.

The patient was admitted to an inpatient psychiatric unit on day 4 after the initial presentation to the ED. At this point, the patient was hyperverbal, irritable, paranoid, and anxious. The patient reported poor sleep, feeling "hypomanic," and endorsed suicidal ideation. The divalproex DR dose was then increased to the home dose of 1250 mg twice daily (see Table 2).

Manic symptoms persisted after 2 days of this regimen, at which point the dose of divalproex DR was increased again to 1500 mg twice daily, and the dose of quetiapine was increased to 600 mg nightly and continued to be titrated up to a final dose of 200 mg in the morning and 600 mg nightly. On day 9 of hospitalization, the patient had a subtherapeutic trough VPA level of 46 μg/mL after 3 days of dosing with 1500 mg twice daily. The patient's divalproex DR dose was increased to 1500 mg in the morning and 2000 mg at night. On day 13, the patient's VPA level increased to 63 μg/mL and symptoms were improving.

Upon consultation with the pharmacist, the patient was switched from a DR product to an IR valproic acid syrup in hopes of more consistent absorption. The dose was reduced to 1000 mg twice daily because of the potential for increased absorption with this formulation. The plan was to obtain a trough level in 3 days; however, the patient was abruptly discharged because a bed became available at a recovery home. The patient was scheduled to follow up with his outpatient psychiatrist within 1 week.

Discussion

The patient presented in this case highlights the variability in drug levels that may occur for patients treated with VPA, including for patients with previous WLS. Although this patient's RYGB procedure had occurred 9 years before this admission, it was believed that the erratic VPA levels were a result of changes to drug absorption. As discussed previously, VPA can be dosed according to weight, with most patients achieving a therapeutic response when dosed from 20 to 30 mg/kg/day. The anticipated dosing range for this patient (89 kg) was between 1780 and 2670 mg/d (max 5340 mg/d). The dose of VPA before admission was 2500 mg/d, representing a weight-based dose of 28 mg/kg/day. The level obtained upon admission, which was likely close to a trough level, was 61.2 μg/mL. The next trough level obtained was significantly lower at 46.0 μg/mL, despite a dose increase to a TDD of 3000 mg VPA per day (32 mg/kg/day). The third level obtained was very close to the initial level at 63.0 μg/mL, despite a VPA dose increase to 3500 mg/d (39 mg/kg/day). There was no concern that the patient was attempting to avoid taking the medications ordered during admission (ie, "cheeking" medication). The unexplained changes in level were instead attributed to the erratic absorption associated with the previous WLS.

Previous case reports have demonstrated that drug absorption can still be impacted by WLS many years after the procedure.[19,20] In 1 analysis, the authors demonstrated that approximately 25% of patients taking oral anticancer medications after WLS had plasma concentrations below the expected level. Four patients in this sample who had undergone RYGB surgery more than 5 years before the assessment (range 5-9 years) experienced subtherapeutic levels to 4 different oral anticancer medications.[19] Another report describes 2 cases of patients with hepatitis C who experienced treatment failure with direct-acting antiviral therapy 14 and approximately 20 years after RYGB, respectively.

The authors concluded that this was due to the pH changes caused by WLS, as these medications are better absorbed in an acidic environment.[20]

VPA is a basic, lipophilic anticonvulsant medication that may also be less soluble with decreased absorption after these pH changes.[21] Few reports have been published describing the impact of WLS on anticonvulsant efficacy. One available case of a patient with epilepsy demonstrates the significant impact that WLS can have on levels of some anticonvulsants, including VPA. The dose of VPA for this patient had to be increased from their presurgery (RYGB) TDD of 3000 mg (19 mg/kg/day) to a final TDD of 6000 mg (38 mg/kg/day) by 1.5 years postsurgery. Despite this dose increase, the reported trough levels decreased from 83 to 62 μg/mL in this timeframe. This patient also required a postsurgery increase in phenytoin dosing due to subtherapeutic levels.[21]

There have been 2 published case reports on the acute use of intravenous (IV) VPA in patients after undergoing WLS.[22,23] One case report describes treatment with IV VPA for severe mania in a patient with schizoaffective disorder.[22] The patient had been started on a TDD of 2000 mg IV VPA (7 mg/kg/day), which was titrated up over the following 3 days to a TDD of 4000 mg (14 mg/kg/day) with a resulting VPA level of 77.4 μg/mL. The following day, the patient was switched to VPA oral syrup and was titrated up to a TDD of 5000 mg (18 mg/kg/day) over the following days with a resulting VPA level of 118.1 μg/mL. The other case report describes the use of IV VPA for a patient with bipolar disorder who was not expected to take medications orally for at least 1 month after WLS. The patient was started on a TDD of 750 mg IV VPA (equivalent to the home dose the patient was taking before surgery). Five days after initiating this regimen, a VPA level of 34 μg/mL was obtained.[23] Both of these case reports highlight the potential effectiveness of IV VPA in treating patients acutely after WLS; however, the long-term effects on its safety and efficacy have yet to be studied. The logistical requirements to consistently administer IV VPA may also limit its use to the inpatient setting.

In the case presented here, the decision was made to switch the patient from the divalproex DR formulation to the IR formulation of valproic acid syrup. While there are limited data available evaluating the ER formulation of VPA for patients with intestinal malabsorption after WLS, it is sometimes recommended to avoid ER formulations of antiseizure medications because of the expected decreased absorption.[21] It has been demonstrated that VPA syrup has the fastest rate of absorption, highest Cmax, and shortest time to Cmax (tmax) when compared with the 4 other formulations of VPA/divalproex available in the US.[24]

One limitation of this case is the lack of previous VPA levels for comparison, despite treatment with the ER formulation of VPA for approximately 1 year and then treatment with the DR formulation for approximately 1 month before admission. Therefore, it is unknown if the patient previously experienced the erratic levels demonstrated on this admission. In addition, a free valproic acid level was not obtained, which can be helpful in the setting of hypoalbuminemia.[25] The patient presented here did have an albumin level slightly below the normal range. It should be noted that RYGB procedures are not known to cause hypoalbuminemia, so this may have been due to nutritional deficiencies or another cause.[26,27]

Although the patient clinically improved by the end of the hospital admission, it would be difficult to attribute this to the VPA, given that the trough level was essentially unchanged from the level obtained at admission. The improvement in manic symptoms was instead most likely due to the titration of the quetiapine from the home dose of 350 mg nightly to a dose of 200 mg in the morning and 600 mg nightly (800 mg/d). There is also the possibility that the patient had used substances, such as methamphetamine, closer to the time of admission than what he initially reported, which could have contributed to the symptoms present on admission.

Conclusion

WLS can create significant changes to the absorption, dissolution, and concentration of mood stabilizers, such as VPA, making it vital that providers are cognizant of these effects. Previous case reports have demonstrated that WLS, including RYGB, may continue to impact PK parameters for many years after the procedure. For the patient presented here, much higher doses of VPA than expected based on weight were required to reach the therapeutic range. While the team did decide to ultimately switch the patient to an IR product for better absorption, no further levels were drawn to evaluate the impact of this modification because of the rapid hospital discharge. This highlights the need for the treatment team to consider more frequent levels for patients with a history of WLS compared with the general patient. If close monitoring of drug levels cannot occur, an alternative first-line treatment option may be considered for the management of bipolar disorder. An opportunity for future research would be to further investigate whether the IR formulation of valproic acid is preferable for the management of bipolar disorder after WLS, as the current literature focuses on patients with seizure disorders.

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