Antiseizure Medication use in Gastric Bypass Patients and Other Post-Surgical Malabsorptive States

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Article Info

Article history:
Received 16 November 2020
Revised 25 February 2021
Accepted 28 February 2021
Available online 22 March 2021

Keywords:
Gastric bypass
Antiseizure medications
Anticonvulsants
Malabsorption
Pharmacokinetics

Abstract

Healthcare professionals are encountering an increasing number of patients who have undergone bariatric surgeries. Antiseizure medications (ASM) have a narrow therapeutic window, and patients with malabsorptive states receiving ASM present a complex situation as the pharmacokinetics of these drugs have only been studied in patients with a normal functioning gastrointestinal tract. Patients with malabsorptive states may have altered pharmacokinetics, and there is limited literature to guide drug selection and dosage adjustment in patients with malabsorptive states. This review highlights pharmacokinetic parameters of common ASM, and considerations when managing patients on them. The effect of pH, lipophilicity, absorption, and metabolism should be taken into account when selecting and managing ASMs in this patient population. Based on these parameters, levetiracetam, and topiramate have fewer issues referable to absorption related to bariatric surgery while oral formulations of phenytoin, carbamazepine, oxcarbamazepine and valproic acid have reduced absorption due to effects of bariatric surgery based on the pharmacokinetic properties of these medications. Extended formulations should be avoided and ASM serum concentrations should be checked before and after surgery. The care of patients with epilepsy who are scheduled to undergo bariatric surgery should be guided by a multidisciplinary team including a pharmacist and a neurologist who should be involved in the adjustment of the ASMs throughout the pre-surgical and post-surgical periods.

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https://doi.org/10.1016/j.ebr.2021.100439
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Introduction

The prevalence of obesity in the United States is 39.8%, with an annual medical cost of $147 billion in 2008 [1]. One of the treatment options for obesity, particularly for morbid obesity (BMI > 40), is bariatric surgery. The number of bariatric procedures has increased worldwide. In 2017 it was estimated that 228,000 bariatric surgeries were performed in the United States [2].

Bariatric procedures and malabsorptive states, in general, may alter the absorption, dissolution, metabolism and bioavailability of antiseizure medications (ASMs). In addition, weight loss associated with these procedures can also lead to changes in the pharmacokinetics of ASMs. These changes may lead to clinically relevant changes of ASMs and can lead to loss of seizure control or toxicity. A population based study found that approximately 30–45% of obese patients (BMI > 30) were receiving central nervous system drugs, antimicrobials, cardiovascular agents or agents for musculoskeletal diseases over a period of 18 months [3]. Furthermore, a study evaluating drugs taken in bariatric surgery patients found that approximately 14% were on ASMs drugs prior to their procedures [4]. Although it is not uncommon for patients on ASMs to undergo bariatric surgery there is very little data to guide the adjustment of antiseizure therapy in these situations [5–7].

A recent case prompted our interest in evaluating dose adjustments and selection of ASMs in patients with malabsorptive states. This review aims to evaluate pharmacokinetics alterations of common ASMs after various gastric bypass procedures and malabsorptive states.

### Table 1

|                      | Pre-Surgery | 2 weeks Post-Operative | 5 weeks Post-Operative | 9 months Post-Operative | 10 months Post-Operative | 11 months Post-Operative | 1 year Post-Operative | 1.5 years Post-Operative |
|----------------------|-------------|------------------------|------------------------|-------------------------|--------------------------|--------------------------|------------------------|--------------------------|
| Patient's weight (kg)| 156         | 148                    | 100                    | 200 mg BID              | 200 mg BID               | 250 mg BID               | 250 mg BID             | 250 mg BID               |
| Phenytoin Dose       | 7           | 5.8                    | 8.5                    | 13.1                    | 1.5                      | 1.1                      | 1.4                    | 1.6                      |
| Therapeutic range:   | 10–20 mcg/mL|                       |                        |                         | 1 mg/mL                  |                         | 1–2 mg/mL             |
| Valproic Acid Dose   | 1000 mg TID | 1000 mg TID            | 1000 mg TID            | 1000 mg TID             | 1500 mg TID              | 1750 mg TID             | 1500 mg QID            |
| Therapeutic range:   | 50–125 mcg/mL|                      |                        |                         | 40–60 mcg/mL             |                         | 40–60 mcg/mL           |
| Free Valproic Acid   | 9           | 15                     | 13                     | 4                       | 3                        | 4                        | 5                      | 5                       |
| Therapeutic range:   | 5–25 mcg/mL |                      |                        |                         | 5–25 mcg/mL              |                         | 5–25 mcg/mL            |

*No patient weight, phenytoin levels were not available for 10 months, 11 months, and 1 year post-operatively. Abbreviations: Kg: kilogram, BID: Twice a day, Mcg: microgram, ml: Milliliters, TID: Three times a day.

**Patient case**

A 38-year-old female with well controlled genetic generalized epilepsy manifested exclusively by generalized tonic-clonic seizures, presented to epilepsy clinic for recommendations involving ASM prior to a Roux-en-Y gastric bypass surgery. Preoperatively she had a weight of 156 kg and a BMI of 58 kg/m² and her seizures were well controlled, being seizure-free for approximately 8 years. Her ASM included valproic acid delayed release tablets 1500 mg twice a day (BID) and phenytoin extended release capsules 200 mg BID. Since the patient was seizure-free for 8 years, and tolerated phenytoin and valproic acid, she remained on these medications despite known drug interaction [8]. In preparation for the procedure her ASM were changed to immediate release formulations and included: valproic acid capsules 1000 mg three times a day (TID) (19.2 mg/kg/day) and phenytoin immediate release tablets 200 mg BID (2.6 mg/kg/day). Prior to the change in formulations of her medications it was reported her valproic acid concentrations were within the normal range, and her total and free phenytoin concentrations were 12.2 mcg/mL (reference range: 10–20 mcg/mL) and 2.2 mcg/mL (reference range: 1–2 mcg/mL), respectively. Her ASM concentrations after the change and prior to surgery were within the therapeutic ranges and are shown in **Table 1**. The patient subsequently underwent the surgery and her drug concentrations two weeks after the surgery are also shown in Table 1. Since her free phenytoin concentration was decreasing, her phenytoin was subsequently increased to 250 mg BID. Her repeat total and free phenytoin concentrations (3 weeks later, 5 weeks post-operatively) were 8.5 mcg/mL and 1.4 mcg/mL, respectively. The phenytoin dose was not changed further given...
the free concentration was deemed therapeutic. The patient's weight at 6 months post-surgery had decreased to 126.6 kg. The patient followed-up approximately 9 months post-operatively with serum drug concentrations that are shown in Table 1. Due to a decreased valproic acid concentration her valproic acid was increased to 1500 mg TID. Her valproic acid dose was increased further to 1750 mg TID and eventually to 1500 mg four times a day (QID). During her visit 1.5 years after her surgery her BMI was 32.4 and her weight was 87 kg. Her serum ASM concentrations are shown in Table 1. Due to a slightly high free phenytoin level, her dose was decreased to 200 mg BID. She was ultimately maintained on 200 mg BID (4.6 mg/kg/day) of phenytoin and 1500 mg QID (68.9 mg/kg/day) of valproic acid.

Types of bariatric surgeries

Bariatric surgeries are classified into three categories: restrictive (limiting stomach size or structure), malabsorptive (shortening intestinal length or modifying gut anatomy), and combination of restrictive and malabsorptive. Restrictive proce-
Pharmacokinetic parameters of oral antiseizure drugs.

Table 2

| Medication       | pKa       | Lipophilicity (LogP) | Intestinal Metabolism | Active Transport Pumps | Enterohepatic Recirculation | Approximate Bioavailability/ Site of Absorption | Impact of Food on Absorption | May be Largely Affected by Malabsorptive Procedures |
|------------------|-----------|----------------------|-----------------------|------------------------|----------------------------|-----------------------------------------------|-------------------------------|-----------------------------------------------|
| Carbamazepine    | 16.0, 13.8| 2.7                  | Substrate CYP3A4 (to active metabolite carbamazepine-10,11-epoxide) | –                      | Yes                        | 70 – 79%                                      | None with slow release formulation            | Yes                                            |
| Phenytoin        | 9.5, 2.3  | 5.87                 | Substrate of CYP2C9, CYP2C19, CYP3A4 (inactive metabolites) | –                      | –                          | 100%                                          | None                                         | Yes                                            |
| Levetiracetam    | 14.9, 9.9 | 1.9                  | Substrate of UGT1A4 and UGT2B7 | –                      | –                          | 100%                                          | May delay absorption by 0.5 hours, but extent is not affected | No                                             |
| Oxcarbazepine    | 13.2, 11.4| 1.8                  | Substrate of CYP3A4 and UGT to 10-Hydroxy-10,11-dihydro carbazepine | –                      | Possible                   | 80% – 80%                                     | None                                         | Yes                                            |
| Phenobarbital    | 9.5, 2.3  | 5.87                 | Substrate of CYP2C9, CYP2C19, CYP2E1 | –                      | Yes                        | 80% – 80%                                     | Increased absorption/no change with food | Yes                                            |
| Topiramate       | 11.9, 3.7 | 0.6                  | –                      | –                      | –                          | 80–90%                                       | Caution with tube feeds                       | None                                          |
| Valproic Acid    | 5.14, 2.5 | 2.5                  | UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B15 | –                      | Yes                        | 90% – 90%                                     | None                                         | No                                             |

Abbreviations: CYP: Cytochrome, UGT: Urindinediphosphate, glucoronosyltransferases, ABC: ATP-binding cassette protein B1, SLC: solute carrier family 22, member 1 PgP: P-glycoprotein.
limited data available to guide therapy for patients on ASMs. Therefore, pharmacokinetics parameters should be taken into consideration when selecting and dosing ASM in patients with malabsorptive states. The pharmacokinetics of medications through the GI tract can be divided between the stomach and small intestine. The stomach is responsible for dissolution, while the small intestine is responsible for absorption, transport, and metabolism. The small intestine has a larger surface area and more permeable membranes, leading to increased drug absorption in comparison to the large intestine [12]. Alterations in the GI anatomy can alter the pharmacokinetics at either of these sites [7,13]. It is important to note that these proposed mechanisms are based on pharmacokinetic modeling, and further investigations are needed in patients with malabsorptive states.

Effect of pH

The intraluminal pH of the stomach is normally acidic with a pH of 1.5 to 3.5 while the pH of the small intestine is 6.6 to 7.5 and increases rapidly beyond proximal duodenum to peak at 7.5 in the distal ileum [14–15]. After partial or total gastrectomy, as with some bariatric surgeries, the available parietal cells that secrete hydrochloric acid may be reduced or bypassed leading to an increase in gastric pH [13]. This may cause basic drugs to be less soluble and therefore have decreased dissolution. Conversely, acidic drugs may have uncharged or a slight increase in absorption [13,16]. The acid-base behavior of ASM is multifaceted as some medications have multiple functional groups, and therefore, multiple pKa values. The pKa of common ASM medications are listed in Table 2.

Absorption

Most ASM are absorbed in the small intestine due to its large surface area [17]. Depending on anatomy or underlying malabsorptive condition, small intestinal transit time for drugs may be accelerated and therefore lead to decreased absorption. There is limited literature evaluating extended release formulations in patients with intestinal malabsorption, but they are routinely avoided because absorption is expected to be diminished; thus, it is generally recommended to switch to immediate-release formulations to maximize absorption in these patients [13,17–18]. Food and nutritional support may also impact medication absorption, and the impact of absorption of ASMs with food is listed in Table 2.

Lipophilicity

Lipophilicity can also affect drug absorption. After RYGB there is a delay and reduction in bile secretion [13,17]. Highly lipophilic drugs may be more affected because they often depend upon bile acids to enhance solubility. A higher logP indicates a drug is lipophilic, while a lower logP indicates a drug is hydrophilic. In patients with malabsorptive states compared with lipophilic drugs, the impact on altered absorption may be less affected for more hydrophilic drugs (i.e. a drug with lower logP) given it does not need bile acids to facilitate its absorption [16]. An optimal logP for dissolution and passive diffusion across the intestinal membrane is 1–2 [16]. The lipophilicity of common ASM is shown in Table 2.

First pass metabolism

Due to a reduction in the length of the small intestine in malabsorptive state enzymes and carrier proteins may be affected [13]. Before drugs reach the liver and plasma, they may encounter enzymes in the intestinal mucosa, particularly cytochrome (CYP) P450 enzymes. CYP enzymes play a role in drug metabolism and can produce inactive and active metabolites. The majority of CYP enzymes are located in the liver; however some are located in the small intestine, the most prevalent of which is CYP3A4, accounting for 80% of intestinal CYPs [19]. Generally, the proportion of CYP enzymes is higher in the proximal regions of the small intestines, which may be bypassed in bariatric surgery and other malabsorptive states [19]. In addition to CYP enzymes, urindinediphosphate, glucuronosyltransferases (UGT), phenylsulfotransferases (PST), and glutathione S-transferases (GST) are present in the small intestine and may also affect metabolism. Decreased exposure to these intestinal enzymes may cause variable pharmacodynamic effects depending on the specific drug: increased drug activity may result from decreased metabolism to inactive metabolites or decreased drug activity may result from increased metabolism to active metabolites. Table 2 indicates drugs that may be susceptible to intestinal metabolism by CYP, UGT, PST, or GST enzymes. A common example of this with ASMs is the inhibition of CYP3A4 by grapefruit juice, leading to increased concentrations of carbamazepine [20]. Of note, there is insufficient understanding about the extent to which these drugs have intestinal metabolism. Also, the GI tract can adapt over time, and changes in drug concentrations for medications with intestinal metabolism may be transient [13].

Drug absorption

ASM can move across the intestinal membrane to the plasma via passive diffusion or active transport. Numerous active transport pumps are found primarily in the jejunum and small intestine [17,21]. These transporters include organic anion transporting polypeptides (OATP2B1, OATP1A2), monocarboxylic acid transporter 1 (MCT1), and oligopeptide transporter (PEPT1) [21]. If the medication undergoes active transport via these pumps, less drug may reach the plasma when exposure to the pumps is diminished after intestinal resection. ASM with active transport pumps are shown in Table 2.

Additionally, medications may be affected by efflux pumps, such as P-glycoprotein (Pgp), breast cancer resistance protein (BCRP) and multi-drug resistance associated protein (MRP2). These efflux pumps are located in the intestinal epithelial cells and they transport drugs from the blood into the intestinal lumen, thereby decreasing the drug plasma concentrations. In patients with malabsorptive anatomy there may be a decrease in these efflux pumps, which might lead to a subsequent increase in plasma concentration of the drug [16].

Enterohepatic recirculation

Lastly, some drugs undergo enterohepatic recirculation. In patients with a functional intestinal tract drugs may re-enter the duodenum for repeated absorption after circulating through the liver. In patients with RYBG this surface area is reduced, potentially leading to a cycle of decreased absorption [16]. Drugs that undergo enterohepatic recirculation are listed in Table 2. In post-surgical malabsorptive states these drugs may have decreased absorption.

Collectively, all these factors may affect concentrations of the medications in patients with malabsorptive anatomy. Predicting drug absorption, dissolution, metabolism, and transport in patients with malabsorptive states is complex and therefore drug concentrations should be closely monitored. The true extent of the clinical impact these pharmacokinetic factors have on drug absorption in malabsorptive states remains unknown, and more studies are warranted.
Pharmacokinetic changes from weight loss

In addition to pharmacokinetic factors that are affected by anatomical changes, there are numerous pharmacokinetic alterations that may occur after bariatric surgery because of the physiological changes related to the resulting weight loss. The volume of distribution (Vd) is the hypothetical distribution of drug into tissues outside the vascular system [22]. Vd can be affected by both adipose tissue and protein binding [17]. As patients lose weight their adipose tissue decreases. The resulting alterations in Vd are dependent on specific drug properties, particularly lipid solubility. Lipid soluble drugs will deposit in the adipose tissue. For these drugs, the concentrations in the plasma will increase as the tissue concentration in the adipose tissue decreases if patients lose weight. The contrary is true for water soluble or hydrophilic ASM, which will stay in the vascular space despite changes in adipose tissue post-surgery [22]. Deposition into adipose tissue is also dependent on protein binding [17]. It is unclear how drug-protein binding is affected after weight loss. Major proteins that bind to drugs include albumin and α-1-acid glycoprotein (AAG). It postulated that AAG may be reduced following weight loss, which would lead to increased free active drug; however, the true extent of this phenomenon is unknown [23].

Practical considerations

Patients with malabsorptive states are at increased risk of altered drug absorption. Given the lack of literature to guide selection of ASMs, pharmacokinetic factors may be considered when selecting and optimizing ASMs in patients with malabsorptive states. ASMs with the following attributes are less likely to be associated with dosage and pharmacokinetic issues following bariatric surgery: acidic properties, lower log P (i.e. more hydrophilic), minimal intestinal metabolism and transportation through efflux pumps, and lack of enterohepatic recirculation. Based on these pharmacokinetic factors the following ASMs show these attributes: levetiracetam and topiramate. Levetiracetam and topiramate both have a low log P, do not undergo intestinal metabolism, enterohepatic recirculation, or transport through active transport pumps. By contrast, the following ASM do not have these properties (basic, higher log P (more lipophilic), intestinal metabolism, transport through transport pumps, and enterohepatic circulation) and are likely to be associated with pharmacokinetic issues following bariatric surgery: phenytoin, carbamazepine, oxcarbazepine, and valproic acid. The extent to which each of these respective pharmacokinetic factors impacts clinical efficacy and toxicity remains unclear. Patient specific factors should always be taken into consideration when selecting and adjusting ASMs. Additionally, delayed-release and extended release formulations are less optimal, and immediate release formulations are generally preferred. Attentive drug monitoring is imperative including frequent concentration checks, particularly in the early post-operative phase.

Very few reports have described the effect of bariatric surgery and other post-surgical malabsorptive states on ASM efficacy. A study compared absorption and elimination of phenytoin in seven patients who had undergone JIB with nine controls. The half-life and absorption of phenytoin was decreased in the patients who had undergone JIB [24]. As previously mentioned, JIB is no longer a procedure of choice for weight control. In addition, there is a case report of undetectable phenytoin concentrations post RYGB despite adequate concentrations before the surgery [25].

Due to the complexities of pharmacokinetic factors and the narrow therapeutic window of ASMs, patients with epilepsy are at increased risk of having recurrent seizures after the gastric bypass surgeries or development of malabsorption states. In addition to the complexities that malabsorptive states have on ASMs, drug interactions (enzyme induction, enzyme inhibition, and competition for protein binding) as seen in patients with a normal functioning GI tract need to be considered. Optimal care for these patients requires a pharmacist and a neurologist working together as part of a multidisciplinary team from before until after the surgery. Close collaboration with the surgeon – to understand the patient’s anatomical changes –is essential. Key considerations to keep in mind listed on Table 3. ASM therapeutic drug monitoring (TDM) plays a critical role in the management of these patients, and ASM concentrations should be monitored frequently. We recommend that these concentrations should be checked weekly for the first 4 weeks, then monthly for the next 3 months if stable. These intervals need to be adjusted if problems with maintaining stable concentration are identified in an individual patient. For patients on stable ASM regimens, concentrations should be collected prior to surgery to determine the therapeutic concentration(s) that have been successful in controlling the seizures, and such concentrations can be used as a target post-operatively. Given the altered protein binding in patients with malabsorptive states, free concentrations of valproic acid and phenytoin should be monitored in addition to total concentrations [26–28]. If adequate concentrations cannot be obtained or there is concern for particularly poor absorption, intravenous medications can be given in the short term for those ASMs with a parenteral dosage formulation. Parenteral administration may temporarily mitigate some of the post-operative pharmacokinetic changes. Once stable, transition to oral medications can be accomplished with close TDM. After discharge from the hospital close follow-up with a neurologist and additional assistance from the pharmacist to monitor and adjust ASMs is always recommended.

In our index case, the patient had a significantly altered GI tract due to her laparoscopic Roux-en-Y gastric bypass surgery. There are multiple factors that may have contributed to alterations in her serum ASM concentrations. She initially had therapeutic concentrations of phenytoin and valproic acid and her drug formulations were switched from sustained release to immediate release.

Table 3

| Take Home Points |
|------------------|
| - Patients with epilepsy undergoing bariatric surgery (or extensive intestinal resection) should be followed by a multidisciplinary team including a pharmacist and a neurologist. |
| - Consider switching oral antiseizure medications (ASMs) to intravenous formulations (if available) when adequate concentrations cannot be obtained, or there is concern for poor absorption in the early post-operative period |
| - Serum ASM concentrations should be frequently checked before and after surgery. We recommend checking levels weekly for the first 4 weeks then monthly for the next 3 months if stable. Intervals need to be adjusted if problems with maintaining stable levels are identified |
| - Upon discharge, ensure close follow up to monitor ASM levels |
| - Extended release formulations should be avoided |
| - Administration of the ASMs directly into the small bowel (i.e. bypassing the stomach) via jejunal tube should be considered |
| - Pharmacokinetic factors should be considered when selecting and adjusting ASMs |

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Subsequently after the surgery she required frequent drug concentration assessment, and her doses of both ASM were increased to maintain therapeutic concentrations despite her weight and BMI being reduced. It also must be noted, enzyme interactions can also affect serum drug concentrations when phenytoin and valproic acid are used in combination. This combination also leads to alterations in protein binding, with valproic acid displacing plasma bound phenytoin [29–31]. Given the complexity of this drug combination in addition to the pharmacokinetic complexities of malabsorp- tive states, it is imperative to follow serum drug concentrations when using phenytoin and valproic acid in combination. The challenges of ASM management after bariatric surgery are outlined by our case report.

Conclusion

We describe issues associated with a patient undergoing bariatric surgery while on ASM. As the number of patients undergoing gastric bypass procedures increases, it is imperative to consider the pharmacokinetic changes in patients with post-surgical malabsorp- tive states. Pharmacokinetic changes should also be antici- pated after non-bariatric surgery resulting in malabsorptive anatomy. This is especially important in patients undergoing sur- geries involving gastrectomy or those leading to short bowel syndro- me. Patients dependent on ASMs for the management of epilepsy present a particularly challenging situation given the nar- row therapeutic index of many of these agents. Close attention to the pharmacokinetic properties of ASM and careful monitoring of serum drug concentrations is important in guiding optimal ther- apy for these patients.

CRediT authorship contribution statement

Caitlin S. Brown: Conceptualization, Methodology, Investigation, Writing - original draft. Alejandro A. Rabinstein: Conceptualization, Methodology, Writing - review & editing. Erin M. Nystrom: Methodology, Investigation, Writing - original draft. Jeffrey W. Britton: Investigation, Writing - review & editing. Tarun D. Singh: Conceptualization, Methodology, Investigation, Writing - original draft.

Declaration of Competing Interest

JWB is a consultant for UCB pharmaceuticals (investigational drug discussion, Rozanolizumab) and a Co-investigator (unpaid) for: 1) GW Pharma, A double-blind, randomized, placebo- controlled study to investigate the efficacy and safety of cannabidiol (GW420043-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures, and 2) Grifols Pharmaceuticals, A Randomized Double Blind Placebo Controlled Study of IVIG in Patients with Voltage Gated Potassium Channel Complex Antibody Associated Autoimmune Encephalitis.

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