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NOAC dosing in patients after Roux-en-Y gastric bypass surgery

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The University of Toledo

2016

Dedication

I would first like to thank my husband, AJ for supporting me through this very difficult endeavor as a non-traditional student, never wavering and always loving.

I would also like to thank AJ Farah for believing in me, when I did not necessarily believe in myself or my capabilities.

I want to thank my family for always being encouraging and caring, especially in the absence of my irreplaceable and loving mother.

Acknowledgements

I would like to thank Kathie Hagmeyer, PharmD, for all of her assistance with my scholarly project, for taking time out of her busy work and even busier home life to make my paper a success and hopefully publish in JAAPA. She has always been an inspiration to me as a pharmacist, a colleague, a family woman, a runner and a friend. I have so much respect and admiration for the person that she is and what she has accomplished in life. She has helped me to remain inspired during the writing of my paper, always encouraging and positive. I am very excited about our subject and Kathie has aided in keeping me grounded and focused. I could not have done it without her!!

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia (Desai, 2013) with a prevalence near 10%. It is the dominant cause of ischemic stroke (cardioembolic) and stroke caused by AF is one of the primary sources of adult disability and death (Mani, 2014). The prevention of stroke in patients with AF is the key to treatment strategy and has become more promising with the evolvement of the novel oral anticoagulants (NOAC). There are many factors that play a significant role in dosing of these agents, one being obesity. Incidentally, thromboembolism is also a frequent complication in patients with morbid obesity (Malmann, 2013).

Obesity has become a challenge for health care and an epidemic in America that continues to rise, hovering above 30% of the total population (Flegal, 2012). It is associated with many comorbid factors such as cardiovascular disease, atrial fibrillation, type II diabetes, dyslipidemia, obstructive sleep apnea, osteoarthritis and depression. Conventional therapy for obesity, such as dieting and medication, have been shown to be ineffective options for long term weight loss in some individuals and has led many to surgical interventions. Several options exist for bariatric weight loss, however, the most common, successful and popular choice is the Roux-en-Y gastric bypass (RYGB) procedure. It has been proven to reduce the most weight, in the least amount of time, reverse comorbidities and produce effective long-term results (Lutz, 2014).

Obesity's strong association with thromboembolism and atrial fibrillation places patients in an equivocal position regarding proper dosage of NOACs related to body surface area and change in anatomy caused by RYGB. The complexity of anticoagulation with NOACs arises with the change in the gastric pH and volume and the alteration in the absorption of the medication in the bypassed duodenum, now represented by the ileum. The Roux-en-Y gastric

bypass surgical procedure has both restrictive and malabsorption properties, which is the reason that it is popular and efficacious with the obese population, and a perplexity for anticoagulation (Padwal, 2009).

Method of data collection

Data was collected via PubMed and NCBI with key phrases of Roux-en-Y gastric bypass, absorption of medications after RYGB, atrial fibrillation and RYGB, atrial fibrillation and the NOACs, pharmacokinetics and bariatric surgery, NOACs after bariatric surgery, rivaroxaban and gastric bypass, dabigatran and gastric bypass, apixaban and gastric bypass. Inclusion criteria included cases reported of patients taking NOACs after gastric bypass surgery. No exclusions were made in case review, due to the limited amount of information on this subject.

Anticoagulation

The prevention of stroke in patients with atrial fibrillation has improved in the last few years with the NOAC therapy now available (Lip, 2012). The NOACs, such as the thrombin and Xa inhibitors, are starting to replace the vitamin K antagonists in various populations including the obese, RYGB patients and older adults. The rapid onset of action and predictability of therapeutic levels of the NOACs (Mani, 2014) has increased their utilization among practitioners. Other benefits of the new therapy include fixed dosing, good oral bioavailability (dabigatran is somewhat limited at 6-7%), stable half-life, no routine monitoring and limited dietary and drug interactions (Martin, 2016)(Table 1). In addition to these advantages, the added benefit to safety and efficacy emanates from the extent of protein binding and the targeting of single factors of the coagulation cascade (Mani, 2014), reducing the risk of intracranial

hemorrhage, and producing an equivalent, at minimum, reduction in stroke and systemic embolism, when compared to warfarin (Connolly, 2009), (Granger, 2011), (Patel, 2011).

In an effort to comprehend the implications of the surgery, details of the procedure need to be reviewed with specific attention initially to the anatomy and then to the physiology, how it affects atrial fibrillation and anticoagulation therapy with the NOACs.

The Procedure

The surgery of RYGB can be done open or laparascopic (usually with DaVinci) and is performed by eliminating a portion of the stomach (restrictive) and rerouting the small intestine (malabsorptive) (Figure 1). The surgeon begins by counting his way from the stomach, following along the duodenum (1st portion of the small intestine) just distal to the ligament of Trietz (end of the duodenum), and then separates the proximal jejunum (now termed the biliopancreatic limb) from the mid proximal jejunum (1-2 feet into the jejunum; now termed the Roux limb) with a stapler. The machine fires three rows of staples on both sides of the separation, ensuring proper closure. The distal end of the biliopancreatic limb is then connected to a more distal site of the jejunum, by means of a surgically created passageway and enhanced with sutures (creating the Y in Roux-en-Y; also called the J-J junction), specifically for the addition of gastric/pancreatic enzymes (Smith, 2011). This site of connection is dependent upon the amount of weight loss needed. The stomach stapling occurs next. The size of the functional gastric pouch is reduced to 2 ounces, via similar stapling technique and separated from the remainder of the stomach (this remainder is now the proximal portion of the biliopancreatic limb). The Roux limb (mid-jejunum) is brought up to the newly created stomach pouch and another passageway is surgically

crafted and sutured together (the entire duodenum now bypassed). The results of RYGB are effective immediately following the operation.

Discussion

The change in anatomy itself is the mechanism which makes the surgery so successful. Initially, the reduction of the stomach or gastric pouch, restricts the contents of food intake (Srivanas, 2015) and causes the person to feel full much sooner. In shrinking the size of the stomach, the surface area of the stomach becomes much smaller, resulting in less breakdown of contents by parietal, mucous, G and chief cells, and postponing emptying. With less of these cells, less hydrochloric acid is released, increasing the pH, creating a more alkaline environment and directly affecting solubility of drugs (Smith, 2011) and consequently, absorption.

The other aspect of the operation is the bypass, in which the duodenum, and first part of the jejunum are no longer the functionally absorptive portion of the intestines. The distal jejunum and the ileum have replaced this portion and now play the role of primary incorporator of nutrients and medications. From the duodenum, moving distally to the ileum, there is a natural reduction in the amount of villi or circular folds that create surface area. A consequence of this bypassed portion, similar to the stomach, is that it too, has a large loss of surface area, resulting in less villi and microvilli for absorption (Miller, 2006).

Surgical procedures (like the RYGB) have superfluous outcomes that influence absorption, disintegration, dissolution, and mucosal exposure (Yska, 2015) limiting the wide therapeutic window of NOACs. The absorption of these medications is directly dependent upon the oral bioavailability and protein binding. With the RYGB procedure, there is an alteration in the distribution of transporter proteins/enzymes in the small intestines related to the change in anatomy.

The transporters of drugs, known as P-glycoproteins (P-gP) or efflux proteins, function normally by bringing substrate back into the lumen of the intestine, thereby decreasing

absorption. These proteins are present in the GI tract and determine how much drug will be absorbed into the body after an oral dose. Also found in the GI tract are the cytochrome P450 enzymes (CYPs) which are responsible for drug metabolism. The most abundant CYP is the CYP3A4 (Darwich, 2012). In the intestines, the cytochrome P450 enzymes and p-glycoproteins are inversely proportional, meaning CYPs decrease in expression from proximal to distal and Pgp increase from proximal to distal (Srivanas, 2015). Therefore, after RYGB, there is an increase in P-gP and hence, the potential for a decrease in drug absorption. The multifactorial consequences of bariatric surgery change the exposure of drugs to the P-gPs and the CYPs of the GI tract and thus the oral bioavailability of the NOACs. They play a pivotal role in the degree of medication absorption because most drugs have a predetermined affinity for transporters (Smith, 2011).

There likewise is a concern with the use of NOACs with drugs that have Pgp and CYP interactions. The levels of the NOACs are “potentially” increased when used with medications that inhibit Pgp’s and CYPs and decreased with drugs that enhance these proteins/enzymes (Desai, 2013). In addition to the protein binding and the enzyme activity, the availability of bile acids, decrease in blood flow to the GI tract, volume of distribution and enterohepatic recycling are additional factors that can affect the solubility of medications and alter absorption rates (Padwal, 2009). Therefore drug levels of the NOACs could potentially end up sub or supra-therapeutic. Supra-therapeutic levels can cause GI and intracranial bleeding and sub-therapeutic levels can place patients at risk for clots, emboli and strokes, all of which can be life threatening.

Due to the vast interactions that can ensue, it becomes important then, for the healthcare provider to decide when it is necessary to monitor for efficacy of the NOACs in this population, related to the limited amount of information and studies performed in this group. The thrombin

inhibitor, dabigatran, can be monitored with diluted thrombin time or thrombin clotting time that measures the amount of time it takes for the blood to clot in plasma while on the anticoagulant (Stangier, 2009). The Xa inhibitors, apixaban, rivaroxaban and edoxaban, can be examined via a chromogenic assay, the anti-factor Xa. Prothrombin time (PT) and activated partial (aPTT) are clot based assays that can also be used for evaluation with very limited sensitivity, meaning that they are not specific to any one anticoagulant. In addition, the results are affected by many other comorbid conditions, infection and even half-life of anticoagulants (Muekk, 2013). The thrombin inhibitors having more of an effect on aPTT and the Xa inhibitors on PT (Desai, et al). Heptest is a clot based factor Xa assay that is prolonged with rivaroxaban. Ecarin clotting time (ECT) measures thrombin activity, as does the Hemoclot, both of which can be used to test levels of dabigatran. Prothrombinase induced clotting time (PiCT) is affected by both the thrombin and the factor Xa inhibitors. All of the tests have limitations and sensitivities, which makes their usefulness questionable at best. (Baglin, 2012).

Clinical Review/Case Reports

A single case report was documented in 2013 of rivaroxaban utilization after laparascopic gastric bypass without gastrectomy, and Y-gastro-jejunostomy. The patient was a morbidly obese (BMI 61) 27 year old female with high venous thromboembolism (VTE) risk and recurrent episodes of VTE over the years. While taking a vitamin K antagonist (VKA) (warfarin), her INRs had been relatively unstable, ranging from 1.6-6.0, even though compliance had been adequate on a dose of between 13.5- 18mg weekly. After the RYGB, she had several occurrences of elevated INR levels, bleeding from the skin and mucous membranes and subsequent hospitalizations. The VKA was then discontinued, vitamin K supplementation was administered

and the INR returned to normal. Therefore, due to the inability to tolerate the VKA, the increased risk of VTE, and the need for long term anticoagulation therapy, she was placed on 20mg of rivaroxaban. She was found to have relatively stable plasma concentrations of the medication, measured by the anti-Xa assay, and therapeutic aPTT/INR at several intervals. Plasma concentrations of rivaroxaban and INR levels peaked at 3 hours with a slow decrease until trough levels were noted. After the next dose, again, both plasma concentrations and INR rose, indicating satisfying (therapeutic) drug levels. This case is a high risk VTE patient that had gastric bypass and was placed on a Xa inhibitor. The results were in expected range of published data, which reveals that the dosage of rivaroxaban was not appreciably diminished by bariatric surgery. The medication is lipophilic and has a high oral bioavailability, but also a rather large amount of protein binding, consequently it resulted in therapeutic levels of rivaroxaban. Therefore, the standard dose is absorbed quickly and may be appropriate for morbidly obese patients after RYGB (Mahlmann, 2013).

The second case of oral anticoagulant after gastric bypass is marked as a “caveat emptor”, and may provide more specific information in regards to the atrial fibrillation population. The report is of a 41 year old male admitted to the critical care unit for chest pain while on dabigatran 150mg twice daily and dofetilide for atrial fibrillation (diagnosed 18 months ago) with a report of medication compliance. He had a history of RYGB 21 years ago. This admission, EKG showed normal sinus rhythm, however, a CT scan revealed a saddle pulmonary embolus with a normal aPTT while on dabigatran. A heparin drip was initiated while inpatient and he was discharged on enoxaparin. Normally, dabigatran is absorbed well at the low pH of the stomach or duodenum, which also happens to be areas of less P-gP expression, also enhancing absorption. In this case, due to the RYGB, the P-gP levels were elevated which inhibited

absorption of the dabigatran, reducing the effectiveness. Also, due to the RYGB, the pH levels were higher, thereby lowering absorption. This was evidenced by a normal aPTT during the event, however there was not a prior aPTT on record for comparison, leading to equivocal findings at best. At the time of publication of this article, there were no warnings of potential for limited absorption of NOACs after gastric bypass surgery (Lachant, 2013).

Conclusion

There still remains a perplexity to prescribing the NOACs in patients that have atrial fibrillation or any other risk for thrombosis, after gastric bypass. The changes in anatomy and physiology, with uncertain and varying absorptive qualities, the limited sensitivity of testing available and the two, very powerful, yet opposing cases, make it a challenge for medical professionals to determine the safety of the NOACs in patients with RYGB.

To our knowledge, at the time of this project, these are the only two cases studied and reported of patients on a NOAC after bariatric surgery. The cases are quite different in the type of bariatric surgery, NOAC prescribed and the outcome. The complexity of these examples leads professionals to seek an anticoagulant that is appropriate for a specific patient population, to choose a dose that is safe and to decide whether or not monitoring will need to be performed and at what intervals.

Many more pharmacokinetic studies are needed to review the efficacy and safety of the novel oral anticoagulant absorption in the bariatric population, providing practitioners with better knowledge when prescribing thrombin and factor Xa inhibitors. Until such time, close monitoring, with several assays, is recommended.

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Table 1. Properties of NOACs (Mani, Lindhoff-Last)

	Rivaroxaban Xa Inh.	**Apixaban** Xa Inh.	**Edoxaban** Xa Inh.	**Dabigatran** Thrombin Inh.
Half Life	9-13hrs	8-15hrs	9-10hrs	14-17hrs
Oral Bioavailability	80-100% w/10mg 66% w/20mg fasting	50%	62%	6-7%
Protein Binding	92-95%	87%	55%	35%
Metabolism	Via CYP (30%), CYP3A4/5, CYP2J2	Via CYP (15%), CYP3A4	CYP, Mainly CYP3A4	Plasma and hepatic esterases
Drug Interaction	PgP inhibitors and inducers. CYP 3A4-CYP 2J2 inhibitors	PgP inhibitors and inducers. CYP 3A4-CYP 2J2 inhibitors	PgP inhibitors and inducers. CYP 3A4-CYP 2J2 inhibitors	PgP inhibitors and inducers. PPIs decrease absorption

Table 1. CYP-cytochrome P450 enzyme. PgP-P-glycoprotein. PPI-proton pump inhibitors

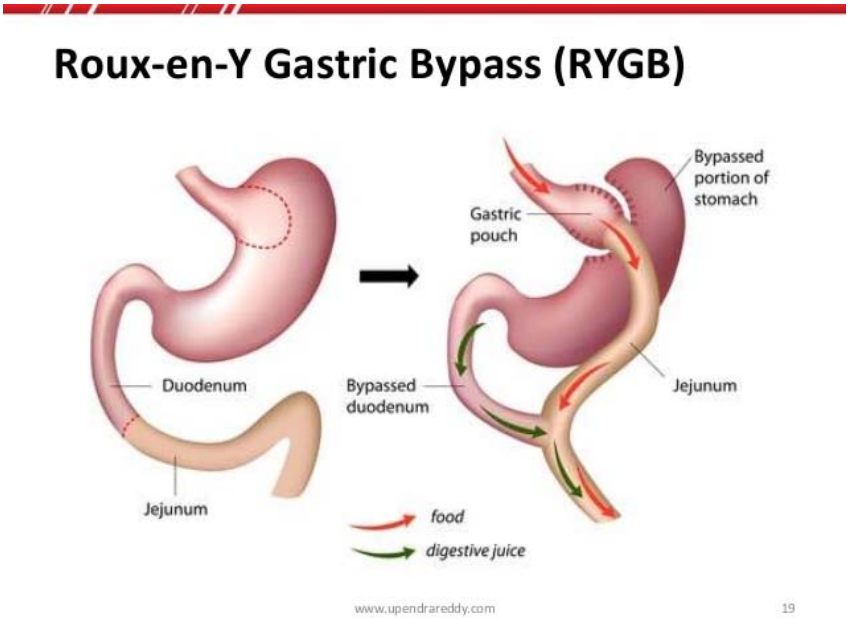

Figure 1: Depicts a drawing of before and after RYGB. The dotted lines are the areas that are surgically severed and anastomosed to create the stomach pouch and bypass of contents of the duodenum into the jejunum. The remainder of the stomach and duodenum are reconnected to the jejunum for vital bile salts and enzymes from pancreas. Source of credit for drawing to Dr. Upendra Reddy

Abstract

As the obesity rates in the U.S. continue to rise, bariatric surgery options have become a health choice for weight reduction and comorbid conditions. The most common of the bariatric surgeries is the Roux-en-Y gastric bypass (RYGB), named for bypassing the duodenum, with a lower portion of the small intestines, thereby inducing malabsorption of nutrients and minerals. The stomach size is also surgically altered, restricting the amount of food that enters. The combination of restriction and malabsorption has proven to be an effective treatment for weight loss, however, the uncertainty of oral drug bioavailability remains a concern for many health care providers. In RYGB patients, there exist several pharmacokinetic factors to consider when prescribing medications, such as the gastric pH, surface area and amount of absorption in the newly formed stomach and modification of small intestines. In addition, knowledge of the biochemical properties of specific drugs can facilitate proper decision making for safety of the patient. Medication dosing in RYGB patients warrants assessment and possible adjustment in order to maintain therapeutic drug levels. With the inception of novel oral anticoagulants (NOACs), replacing warfarin, dosage alteration has become a complicated matter for prescribers, with little to no studies addressing this class, in the presence of altered anatomy (RYGB) and in conjunction with other disease states (atrial fibrillation). The decision to prescribe NOACs continues to obfuscate medical professionals, as the elderly population reaches substantial numbers and bariatric surgery becomes more prevalent. Awareness and education when prescribing NOACs in RYGB patients, including lab monitoring and close follow up for drug modification will ensure safe and appropriate care. More research is needed to determine the oral bioavailability of NOACs after gastric bypass, and until then, accurate administration of them remains presumptive.

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Project Type (Circle one): **Doctoral Project** **Masters Project** **Senior Project**

Complete Title: The dosing of NOAC's in Roux-en-Y gastric bypass patients

Date Completed: 12/9/16 Date Approved: 12/9/16

Date Signed: 12/14/16

one year due to publishing