REVIEW

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Oral Anticoagulant Use After Bariatric Surgery: A Literature Review and Clinical Guidance

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ABSTRACT

Bariatric surgery may alter the absorption, distribution, metabolism, or elimination (disposition) of orally administered drugs via changes to the gastrointestinal tract anatomy, body weight, and adipose tissue composition. As some patients who have undergone bariatric surgery will need therapeutic anticoagulation for various indications, appropriate knowledge is needed regarding anticoagulant drug disposition and resulting efficacy and safety in this population. We review general considerations about oral drug disposition in patients after bariatric surgery, as well as existing literature on oral anticoagulation after bariatric surgery. Overall, available evidence on therapeutic anticoagulation is very limited, and individual drug studies are necessary to learn how to safely and effectively use the direct oral anticoagulants. Given the sparsity of currently available data, it appears most prudent to use warfarin with international normalized ratio monitoring, and not direct oral anticoagulants, when full-dose anticoagulation is needed after bariatric surgery.

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As the prevalence of extreme obesity, defined as a body mass index of $\geq$40 kg/m^2, continues to increase worldwide, so too does the number of bariatric procedures performed: in the US alone, an estimated 200,000 bariatric surgeries are performed annually.[1,2] Clinicians therefore must make management decisions on people who have undergone bariatric surgeries. One such decision is managing therapeutic anticoagulation, because inappropriate anticoagulant drug levels can have serious consequences: thromboembolism if levels are too low, or bleeding if levels are too high.

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In the absence of dedicated studies of oral anticoagulation use after bariatric surgery, clinicians must consider how bariatric surgery affects the absorption and pharmacokinetics of, and hence the efficacy and safety of, oral anticoagulant agents. Herein, we review the available literature on how bariatric surgery affects the disposition of oral anticoagulant agents, and discuss considerations for managing patients who have had bariatric surgery and need therapeutic anticoagulation.

TYPES OF BARIATRIC SURGERY

The term "bariatric surgery" comprises multiple procedures, including adjustable gastric banding (AGB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), and biliopancreatic diversion with duodenal switch (BPD-DS) (Figure 1). As of 2014, sleeve gastrectomy was the most common bariatric procedure performed in the US (51.7%), followed by RYGB (26.8%), revisions (11%), and gastric banding (9.5%).[3] Bariatric surgeries result in weight loss through 1) restriction of caloric intake by reducing the volume of the stomach, 2) malabsorption by reducing the

effective intestinal surface area, or 3) a combination of restriction and malabsorption. SG and AGB are solely restrictive. In SG, a longitudinal resection of the stomach reduces its volume to approximately 60-80 mL, thereby restricting caloric intake.[4,5] In AGB, an adjustable silicone band is placed around the stomach to create a smaller pouch that similarly restricts caloric intake. RYGB and BPD-DS use a combination of restriction and malabsorption. These surgeries differ in the location and connection of the alimentary channel, the biliopancreatic channel, and the common limb. In RYGB, the stomach is stapled to form a 15-30-mL proximal gastric pouch, which is then connected to an alimentary limb of jejunum 75-150 cm distally, resulting in a modest degree of malabsorption.[1] In BPD-DS, the gastric volume is reduced to a lesser degree, and the gastric pouch is reattached more distally to the terminal ileum,[6] which results in a much shorter common channel, a considerable reduction in the absorptive surface, and more significant malabsorption.

CLINICAL SIGNIFICANCE

- Changes in pharmacokinetics and bioavailability of an ingested drug after bariatric surgery are not predictable without dedicated study of individual drugs.
- Limited literature exists on therapeutic warfarin after bariatric surgery and even less on direct oral anticoagulants after bariatric surgery.
- In the absence of dedicated studies, we suggest a vitamin K antagonist as the oral anticoagulant of choice after bariatric surgery given its ability to be monitored and dose-adjusted.

INFLUENCE OF ANATOMIC CHANGES ON DRUG DISPOSITION

The anatomic changes from bariatric procedures have several physiologic effects on drug absorption and resultant bioavailability, which depend on both physiochemical properties of the drug (ie, solubility, degree of ionization, stability, and molecular size)[7] and properties of the gastrointestinal tract (pH, blood flow, intestinal transit time, and surface area for absorption).[6,8]

Reduced Caloric Intake

First, the restrictive nature of the procedures leads to reduced caloric intake, which may impact drugs that require food to increase bioavailability (**Table**).[9-25] Therapeutic doses of rivaroxaban (15-mg and 20-mg), for example, depend on food to increase absorption[18]: the area under the curve (AUC) and peak concentration (C_{max}) of a 20-mg tablet of rivaroxaban increased by 39% and 76%, respectively, with co-administration of food,[21] and the bioavailability of the 15-mg dose of rivaroxaban reached ≥80% when given with food.[19] Thus, the absorption of therapeutic rivaroxaban may be reduced in patients placed on very restrictive diets, which can limit caloric intake to as little as 500 kcal daily after bariatric surgery. However, the bioavailability of apixaban, dabigatran, edoxaban, and warfarin do not appear to be significantly affected by co-administration of food.

Decreased Absorptive Surface

The change in absorptive surface may alter the absorption of drugs as well. The reduced volume for gastric acid secretion leads to a more alkaline pH in the gastric pouch, which could affect pH-dependent drug dissolution and resultant absorption, particularly of drugs that are coated or in controlled-release formulation.[26] Dabigatran, for example, requires an acidic environment for absorption and, therefore, is packaged in capsules containing tartaric acid.[27,28] While an approximately 20% reduction in absorption was seen when dabigatran was given with antacids, this is thought not to be clinically meaningful.[29] The pharmacokinetics (PK) of rivaroxaban, apixaban, and edoxaban are not altered by drugs that increase gastric pH.[21,30,31]

Surgical changes that alter the anatomy of the gastrointestinal tract may affect location of drug absorption, and in the absence of dedicated studies, indirect evidence such as the location of drug absorption (**Figure 2**) can be used to attempt to predict how oral anticoagulant therapy will be affected by bariatric surgery. Apixaban is absorbed primarily in the proximal small intestine, with some gastric absorption and limited colonic absorption.[9,10,32] Rivaroxaban appears to be absorbed primarily in the stomach, as there is reduced absorption (29% decrease in AUC and 56% decrease in C_{max}) when the drug is released into the proximal small intestine, with further reduction as the drug is released more distally into the small intestine and colon.[18] Dabigatran is thought to be absorbed in the lower stomach and duodenum because of the rapid time to peak levels (personal communication with Joanne van Ryn N, 2015). Moreover, a case report showed reduced absorption in short bowel syndrome contributing to insufficient anticoagulation and drug levels below published values of therapeutic doses of dabigatran.[33] Edoxaban is predominately absorbed in the proximal small intestine.[14] While no apparent direct studies of the location of warfarin absorption exist, it is thought to be absorbed extensively in the stomach and proximal small intestine, according to several case series.[34] In one report, patients had prolonged prothrombin times after jejunal and ileal bowel resection[22]; in others, patients with severe short bowel syndrome were able to adequately absorb warfarin (presumably because stomach and duodenum are intact); and in another, a patient who