Administration of Direct Oral Anticoagulants Through Enteral Feeding Tubes

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Jacob J. Peterson, PharmD¹ and James D. Hoehns, PharmD, BCPS, FCCP^{1,2}

Abstract

Objective: To review literature regarding direct oral anticoagulants (DOACs) and determine their viability of administration in solution or via enteral tubes. **Data Sources:** MEDLINE literature searches identified articles published 2007-present using MeSH terms: factor Xa inhibitors, antithrombins, biological availability, and enteral nutrition. Package inserts were included. Manufacturers were asked to provide literature. **Study Selection and Data Extraction:** We included studies emphasizing bioavailability or enteral administration. **Data Synthesis:** Dabigatran and edoxaban package inserts recommend against altering the dosage form, and against enteral administration. One rivaroxaban study was identified. Given with food, enteral administration was comparable to the oral tablet. The mean AUC (0.889, 90% CI 86.12-91.84%) was within the equivalency margins; however C_{max} (0.820, 90% CI 78.84-85.86%) was slightly below the 80% threshold. One apixaban study was identified. They showed bioequivalence between oral and enteral administration in different vehicles, but decreased bioavailability when crushed tablets were given along with nutritional support. AUC and C_{max} were 32% and 19% lower, respectively, when apixaban solution was given via nasogastric (NG) tube with nutritional supplement versus oral administration of solution. **Conclusions:** Dabigatran capsules should not be altered, due to large variations in drug exposure. Rivaroxaban can be given as oral solution or via NG tube. Larger doses must be given with nutritional supplementation and enteral tubes must not be distal to the stomach. Apixaban can be given as oral solution or via nasogastric or gastric tube on an empty stomach. Food impairs bioavailability of the crushed tablets. There are insufficient data to recommend enteral administration of edoxaban and the package insert recommends against altering tablets.

Keywords

factor Xa inhibitors, antithrombins, biological availability, enteral nutrition

Many patients cannot swallow safely or have medical conditions that require the use of enteral feeding tubes for prolonged periods of time. For such patients, medication administration can present challenges. Alternative methods of drug administration may be considered, such as transdermal, rectal, or injectable routes. However, there are limitations in availability, convenience, cost, and patient acceptance with alternative routes. Liquid preparations of medications are frequently unavailable or at times inappropriate. Therefore, the use of oral solid dosage forms delivered through an enteral feeding tube is often used for multiple reasons.¹

Several aspects must be considered before administering medications through an enteral access device. Dosage form, ability to crush, feeding tube size, placement site, and compatibility with enteral nutrition are just a few of many relevant considerations. For a more extensive discussion of medication administration through enteral feeding tubes, interested readers are directed to more comprehensive reviews.¹⁻³

Warfarin is an oral vitamin K antagonist that has been used for years for the prevention and treatment of thromboembolic events. If warfarin is administered through an enteral access device, it is recommended that enteral feeding be held for 1 hour before and after administration.^{4,5} More recently, 4 direct oral anticoagulants (DOACs) have been approved by the Food and Drug Administration (FDA) and are widely prescribed. Dabigatran (Pradaxa) was the first to gain FDA approval in 2010, followed by rivaroxaban (Xarelto) in 2011, apixaban (Eliquis) in 2012, and edoxaban (Savaysa) in 2015. These agents exert their anticoagulant effect by inhibition of the clotting cascade.

¹University of Iowa College of Pharmacy, Iowa City, IA, USA

²Northeast Iowa Medical Education Foundation, Waterloo, IA, USA

Corresponding Author:

James D. Hoehns, Northeast Iowa Medical Education Foundation, 2055 Kimball Ave, Suite 101, Waterloo, IA 50702, USA.

Email: JHoehns@neimef.org

Dabigatran acts as a direct inhibitor of thrombin while the other 3 DOACs are factor Xa inhibitors. As the DOACs have a relatively short half-life, between 5 and 17 hours compared with warfarin, which has a half-life of 20 to 60 hours, it is important that therapy is uninterrupted as any gaps in administration can reduce the degree of anticoagulation. Proper and consistent gastrointestinal absorption must also be ensured with these oral agents to provide adequate anticoagulant effects. We review the 4 DOACs in order of FDA approval date and highlight their differences in formulation, absorption, ability to be altered for oral administration, and recommendations regarding their administration via enteral feeding tubes.

Search Strategy

A MEDLINE search was performed to identify any published study on the administration of DOACs through an enteral feeding tube. The MeSH terms *factor Xa inhibitors*, *antithrombins*, *biological availability*, and *enteral nutrition* were searched along with dabigatran, rivaroxaban, apixaban, and edoxaban. Articles published from January 2007 to February 2016 were considered to ensure all articles were identified. All articles mentioning the administration of these agents through an enteral access device were included. The manufacturers were also contacted and relevant information was requested for all agents.

Dabigatran

Dabigatran etexilate is formulated as a capsule containing drug coated pellets. It is a prodrug that is converted to dabigatran, the active moiety. The capsule pellets contain a tartaric acid core, which creates an acidic microenvironment and increases drug dissolution and absorption.⁶ The oral bioavailability of dabigatran ranges from 3% to 7%. This is increased by up to 75% if the capsule is opened and the pellets are ingested without an intact capsule shell.⁷ This change in overall drug exposure limits the use of dabigatran to patients who can take capsules orally and prevents its use in patients requiring enteral feeding or those unable to swallow the capsule. The manufacturer strictly recommends against altering the capsule shell in any form (see Table 1).⁷

Summary

The capsule must be taken orally and cannot be placed down an enteral feeding tube. The capsule contents cannot be opened, crushed, or altered in any way.

Rivaroxaban

Rivaroxaban is available as a film-coated tablet that may be crushed. If a rivaroxaban tablet is crushed, the manufacturer

recommends mixing the tablet with applesauce to aid in oral administration.⁸ Rivaroxaban was found to remain stable in water (50 mL), juice (50 mL), and applesauce (70 mL) in studies, with 98.5% to 100.7% (relative standard deviation 0.2% to 0.4%) of nondegraded rivaroxaban being recovered for up to 4 hours.^{8,9}

The bioavailability of rivaroxaban is dose dependent and altered based on gastric pH; it has acid-dependent absorption.⁸ Oral bioavailability of the 10 mg rivaroxaban formulation ranges from 80% to 100% and can be taken without regard to food intake.⁸ At higher doses of 15 mg or 20 mg, a lower percentage of the drug is absorbed through the gastrointestinal tract. For these higher doses the bioavailability is decreased if the patient is in the fasting state. Patients receiving 20 mg in the fasting state had an absolute bioavailability of 66%. Administration of the 20 mg dose along with food increases bioavailability (mean area under the curve [AUC] and C_{max} increasing by 39% and 75%, respectively, with food).⁸ To minimize potential for alterations in drug exposure, the 15 mg or 20 mg tablets should be followed immediately by a meal. In a patient unable to tolerate oral feedings, enteral feeding should immediately follow medication administration.

Rivaroxaban has not been found to adsorb to nor be altered by polyvinyl or silicone tubing.⁹ A decrease in 29% of the AUC and 56% of the C_{max} is observed if the drug is administered distal to the stomach.⁸ The difference is thought to be due to its acid-dependent absorption. Due to the potential for differences in drug exposure, the confirmation of enteral tube placement is important prior to rivaroxaban administration. Administration of the drug via feeding tubes should be restricted only to nasogastric (NG) and gastric tubes. Any feeding tube administration bypassing the stomach should be avoided.

A randomized, 3-period, 3-treatment crossover study evaluated 3 dosing strategies of rivaroxaban in 55 healthy adults.⁹ The relative bioavailability of rivaroxaban 20 mg was compared as follows: whole tablet given orally, crushed and mixed with 70 mL of applesauce given orally, and crushed and mixed with 50 mL of water administered via NG tube. All patients received an equivalent 20 mg dose in the fasted state followed by a standardized meal, Osmolite 1.5 Cal, across all study arms. Crushing and administering the tablet orally mixed with applesauce was statistically equivalent to administration of the intact tablet. Both AUC (0.953; 90% confidence interval [CI] = 0.923-0.984) and C_{max} (0.900; 90% CI = 0.861-0.941) were within the accepted 80% to 125% bioequivalence range.⁹ The bioavailability of rivaroxaban administration via NG tube compared to standard oral administration was similar. The mean AUC (0.889; 90% CI = 0.861-0.918) fell within the equivalent range; however, the C_{max} (0.820; 90% CI = 0.788-0.858) was slightly below the lower 80% range.⁹

Table 1. Drug Properties and Recommendations for Administration Through Enteral Feeding Tubes.

Drug	Formulation and Strength (mg)	Mechanism of Action	Indications	Able to Crush and Administer via NG/G Tube	Directions for Administration	Notes
Dabigatran (Pradaxa)	Capsule containing drug coated pellets 75, 110, 150 mg	Direct thrombin inhibitor	<ul style="list-style-type: none"> VTE/stroke prevention in atrial fibrillation DVT/PE treatment and prevention of recurrence 	No	<ul style="list-style-type: none"> Capsule must be swallowed whole 	<ul style="list-style-type: none"> 75% increase in bioavailability if the capsule is opened
Rivaroxaban (Xarelto)	Film-coated tablet 10, 15, 20 mg	Factor Xa inhibitor	<ul style="list-style-type: none"> VTE/stroke prevention in atrial fibrillation VTE prophylaxis post knee and hip replacement DVT/PE treatment and prevention of recurrence 	Yes	<ul style="list-style-type: none"> Stable in 50 mL of sterile water, applesauce, and juice Flushing tubing prior to and after administration is preferable 	<ul style="list-style-type: none"> Acid-dependent absorption 15 mg and 20 mg tablets should be taken with nutrition for consistent bioavailability Absorption not altered by PPIs, H₂ antagonists, or antacids Drug compatible with tubing Avoid administering distal to the stomach Solution may be given orally
Apixaban (Eliquis)	Film-coated tablet 2.5, 5 mg	Factor Xa inhibitor	<ul style="list-style-type: none"> VTE/stroke prevention in atrial fibrillation VTE prophylaxis post knee and hip replacement DVT/PE prevention of recurrence 	Yes	<ul style="list-style-type: none"> Suspend in 60 mL of D5W Suspension should be immediately delivered through NG tube Flushing tubing is preferable 	<ul style="list-style-type: none"> If crushed and administered care should be taken to avoid taking in conjunction with food Drug compatible with tubing Solution may be given orally
Edoxaban (Savaysa)	Film-coated tablet 15, 30, 60 mg	Factor Xa inhibitor	<ul style="list-style-type: none"> VTE/stroke prevention in atrial fibrillation DVT/PE treatment and prevention of recurrence 	No	<ul style="list-style-type: none"> No data to support recommendation 	<ul style="list-style-type: none"> Needs acidic environment to be absorbed

Abbreviations: NG, nasogastric feeding tube; G, gastric feeding tube; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.

Summary

Rivaroxaban is a viable option to be given orally mixed in solution form or with food. Rivaroxaban may also be given to patients via feeding tube if the tube is placed within the stomach. Adequate and timely enteral feedings to coincide with rivaroxaban dosing is also of importance to ensure consistent absorption.

Apixaban

Apixaban is available as a film-coated, immediate-release tablet. Its absolute bioavailability is approximately 50%, and food does not affect its absorption. Apixaban is primarily absorbed in the upper gastrointestinal tract (duodenum, jejunum, and ileum). Direct delivery of apixaban to the distal small bowel results in significantly less drug exposure

compared to that achieved after oral administration.¹⁰ The tablets may be crushed and suspended in 60 mL of D5W and immediately administered through a NG tube. Apixaban is nonionizable, and changes in pH do not affect its aqueous solubility.¹¹ Stability testing has indicated that the medication is stable in both water-based vehicles and applesauce with no significant loss of potency for up to 4 hours postpreparation.¹²

The relative bioavailability (F_{rel}) of apixaban solution or crushed tablet formulations administered by mouth or NG tube was evaluated in a series of 3 separate randomized, crossover protocols involving healthy adult subjects.¹¹ Study 1 (N = 14) compared 2 apixaban 5 mg tablets versus 10 mg oral water-based solution, both administered by mouth. Study 2 (N = 21) compared apixaban 5 mg oral water-based solution by mouth versus 5 mg oral solution via NG tube flushed with either 60 mL D5W or infant formula. Study 3 (N = 21) compared apixaban 5 mg oral water-based solution by mouth versus apixaban 5 mg oral solution via NG tube with a nutritional supplement and versus 5 mg crushed tablet suspended in D5W and administered via NG tube. The geometric mean ratios (GMR) and corresponding 90% confidence intervals were generated for C_{max} and AUC.

In study 1, the F_{rel} of apixaban solution versus tablet was 105% (90% CI = 93.8-117.6) and GMR for C_{max} was 0.977 (90% CI = 0.756-1.261). In study 2, the F_{rel} of apixaban solution administered via NG tube and flushed with D5W and infant formula were 96.7% and 92.2%, respectively, relative to orally administered apixaban solution. Except for C_{max} after infant formula flush (GMR = 0.805; 90% CI = 0.749-0.865), the 90% CI for exposure parameter GMRs fell entirely within the bioequivalent criterion (0.80-1.25). In study 3, the F_{rel} of apixaban crushed tablet administration (suspended in 60 mL of D5W) via NG tube and apixaban solution administered via NG tube in the presence of nutritional supplement were 95.1% and 81.3%, respectively, relative to orally administered apixaban solution. Apixaban C_{max} and AUC were 32% and 19% less, respectively, when apixaban solution was given via NG tube in the presence of nutritional supplement than the corresponding values observed with oral administration of apixaban solution.

Summary

Absorption parameters of apixaban were comparable after oral administration of the tablet and solution dosage forms. The oral tablet can be taken independently of food when intact per the package insert; however, when the tablet is put into solution or given via NG tube, reduced bioavailability and decreased drug exposure is observed if taken with food or nutritional supplementation. If apixaban is administered via NG access, use of a crushed tablet suspended in D5W is preferable to mixing or flushing with nutritional supplement.

Edoxaban

Edoxaban is the most recent agent to gain FDA approval. It is available as a film-coated tablet.¹³ Absolute bioavailability is 62% and food does not affect systemic exposure to edoxaban. No studies have been conducted to assess potential changes in bioavailability when tablets are crushed, mixed into solution, or administered via a feeding tube. Due to the lack of literature, the manufacturer does not recommend that edoxaban be altered in any way before administration.¹³ Given its formulation as a film-coated tablet, it is possible future studies would support the viability of enteral administration of edoxaban.

Summary

Given the current relative paucity of information with edoxaban, it should only be taken as an intact tablet.

Conclusions

For hospitalized patients who require anticoagulation and are receiving enteral nutrition for limited duration, the use of parenteral anticoagulants would seem to be the most practical option. However, some patients may require oral anticoagulation with the DOACs, which include dabigatran, rivaroxaban, apixaban, and edoxaban. Given the current literature, dabigatran and edoxaban are not recommended for any form of enteral administration.

For patients who are receiving rivaroxaban or apixaban and require enteral feeding tubes for longer durations, then administering these medications via enteral access to the stomach is feasible, provided directions for administration are followed. Each medication has only been evaluated with NG enteral access. If the distal tip of the feeding tube is located in small bowel then delivery of either medication via enteral access is not recommended. Neither medication should be directly mixed with enteral nutrition before administration. Indirectly comparing rivaroxaban and apixaban administration via NG access in the presence of nutritional supplement, the absorption of rivaroxaban is less adversely affected than in the case of apixaban. For patients receiving continuous enteral feeding, use of rivaroxaban may be preferred over apixaban, as less interruption in the feeding schedule would be required for drug administration. Information is extremely limited to evaluate whether the administration of rivaroxaban or apixaban via an enteral access device alters their rates of bleeding complications compared with oral administration.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Hoehns was a site sub-investigator for the following

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