Relative Bioavailability of Apixaban Solution or Crushed Tablet Formulations Administered by Mouth or Nasogastric Tube in Healthy Subjects

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ABSTRACT

Purpose: Crushed tablet and solution formulations of apixaban administered orally or via a nasogastric tube (NGT) may be useful in patients unable to swallow solid dose formulations. It is important to understand whether new formulations and/or methods of administration impact apixaban bioavailability and pharmacokinetic properties. These studies evaluated the relative bioavailability (F_{rel}) of apixaban solution administered orally; oral solution administered via NGT flushed with either 5% dextrose in water (D_5W) or with infant formula; oral solution via NGT with a nutritional supplement; and crushed tablet suspended in D_5W and administered via NGT.

Methods: Three open-label, randomized, crossover studies were conducted in healthy adults (study 1: apixaban 10-mg tablet [reference] versus oral solution, both administered PO; study 2: apixaban 5-mg oral solution PO [reference] versus oral solution via NGT flushed with either D_5W or infant formula; study 3: apixaban 5-mg oral solution PO [reference] versus apixaban 5-mg oral solution via NGT with a nutritional supplement and versus crushed tablet suspended in D_5W and administered via NGT). Point estimates and 90% CIs of the geometric mean ratios (GMRs; test/reference) were generated for C_{max} and AUC. Adverse events were recorded throughout each study.

Findings: F_{rel} of the oral solution was 105% versus tablet, and F_{rel} for oral solution via NGT with D_5W flush, infant formula flush, nutritional supplement, and crushed tablet via NGT versus oral solution administration were 96.7%, 92.2%, 81.3%, and 95.1%, respectively. The 90% CIs of the GMRs of all AUCs met the bioequivalence criterion except that of the nutritional supplement (0.766–0.863). The corresponding GMRs for C_{max} were 0.977, 0.953, 0.805, 0.682, and 0.884. For the solution via NGT flushed with D_5W and for the crushed tablet, the 90% CIs of the C_{max} GMRs met the bioequivalence criterion. Apixaban was well tolerated in all 3 studies; most adverse events were mild.

Implications: Comparable F_{rel} was observed for oral apixaban solution, tablet, NGT administration of solution flushed with D_5W and infant formula, and NGT administration of crushed tablet suspension. Exposure was less when oral solution was administered via NGT with nutritional supplement. These results support several alternative methods of administering apixaban that may be useful in certain clinical situations. ClinicalTrials.gov identifiers: NCT02034565, NCT02034578, and NCT02034591. (*Clin Ther.* 2015;37:1703–1712) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: apixaban, bioavailability, crushed tablet, nasogastric tube.

INTRODUCTION

Apixaban is an oral, selective, direct reversible factor Xa inhibitor recently approved for use in the European Union, the United States, and other countries for stroke prevention in patients with atrial fibrillation,[1,2] for thromboprophylaxis after elective hip- or knee-replacement surgery,[3,4] and for the treatment of venous thromboembolism.[5,6] Apixaban is available as film-coated immediate-release 2.5- and 5-mg tablets.[7]

Apixaban is a Biopharmaceutics Classification System Class III compound (high solubility/low

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permeability),[8] and is non-ionizable; thus, changes in pH do not affect the aqueous solubility of apixaban. Given orally, the bioavailability of apixaban tablets is ~50%,[7] and apixaban is absorbed primarily in the upper gastrointestinal (GI) tract, proximal to the colon.[9] The T_{max} of the apixaban tablet formulation is ~3 hours after oral administration in healthy subjects, and the $t_{1/2}$ is ~12 hours (range, 8–15 hours).[10] Elimination occurs through multiple pathways (including renal elimination, metabolism, and biliary and intestinal excretion), with renal clearance accounting for ~27% of total clearance.[11,12]

Dysphagia, or difficulty swallowing, occurs in ~6% to 27% of the elderly population, and pediatric patients ≤5 years of age are often not able to swallow the oral dose formulations.[13–18] Patients with dysphagia may delay taking medication or skip the medication entirely,[19] and clinicians will often seek alternate methods of administration. Under these circumstances, and if a liquid formulation is not readily available, solid oral formulations are often crushed and mixed with liquids or semisolid foods.[20] These extemporaneous manipulations of solid oral dose formulations can significantly impact the pharmacokinetic properties of a drug.

In addition, crushed tablet preparations, as well as liquid formulations, are often administered through a nasogastric tube (NGT), and clinical practices can vary significantly. For example, the administration of a medication via NGT using a flush of 5% dextrose in water (D_5W) may be preferred in infants who have no fluid restrictions, whereas the administration of a medication during an enteral feeding may be preferred in infants with fluid restrictions.[21] Likewise, medication is sometimes administered via NGT in adults who have difficulty swallowing and are receiving enteral nutrition.[22] Therefore, it is important to understand whether the method of administration under these conditions has an effect on the bioavailability and pharmacokinetic properties of a treatment.

Crushed apixaban tablets or an apixaban solution formulation could be useful for patients unable to swallow solid tablets. In in vitro experiments, near-complete apixaban recovery was achieved when apixaban solution was flushed through an NGT (Kendall Entriflex dual-port feeding tube [Covidien, Mansfield, Massachusetts] with a weighted flow-through stylet [10 Fr (diameter), 109 cm (length)]) by D_5W, and crushed tablets were stable in water and D_5W for up to 4 hours (BMS, 2014). Therefore, 3 clinical studies were conducted to assess the relative bioavailability (F_{rel}) of an apixaban oral solution administered orally versus that of apixaban oral solution or crushed tablets administered through an NGT.

SUBJECTS AND METHODS

Study Designs

Study 1 (NCT02034565)

This was an open-label, randomized, 2-way crossover study of single-dose apixaban administered in the fasted state. The primary objective of this study was to compared the F_{rel} of apixaban oral solution with that of a tablet formulation. It was conducted at MDS Pharma Services (Neptune, New Jersey), and the protocol was approved by MDS Pharma Services IRB (Lincoln, Nebraska). Healthy subjects were randomly assigned in a 1:1 ratio to receive a single oral dose of apixaban 10 mg as either 2 × 5 mg tablets or 25 mL × 0.4 mg/mL solution.

Study 2 (NCT02034578)

This was an open-label, 3-treatment, 3-period, randomized, crossover study of single-dose apixaban. The primary objectives of this study were to compare the F_{rel} of apixaban oral solution administered via an NGT flushed with either D_5W or infant formula with that of the oral solution formulation administered by mouth. It was conducted at Parexel Baltimore Early Phase Clinical Unit (Baltimore, Maryland), and the protocol was approved by ASPIRE IRB (La Mesa, California). Healthy subjects received apixaban 5 mg (12.5 mL × 0.4 mg/mL oral solution) administered via oral syringe with 240 mL of water; via an NGT flushed with 60 mL of D_5W, then with 180 mL of water administered orally; and via an NGT immediately followed by 60 mL of infant formula (Similac® Advance® Ready-to-Feed Infant Formula with Iron; Abbott Nutrition, Columbus, Ohio), then with 180 mL of water administered orally.

A 10-Fr, 109-cm Kendall Entriflex dual-port feeding tube (Covidien) with a weighted flow-through stylet was used in this study. The tip of the NGT was placed in the stomach, as confirmed by radiography.

Study 3 (NCT02034591)

This was an open-label, 3-treatment, 3-period, randomized, crossover study of a single dose of