Intra-anal Iferanserin 10 mg BID for Hemorrhoid Disease: A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Background: Despite the prevalence of internal hemorrhoid disease (HD), there are few pharmacologic options. Iferanserin, a selective serotonin receptor antagonist, is being studied for use in the treatment of HD.

Objective: This Phase IIb study evaluated the efficacy and tolerability of 10-mg twice-daily iferanserin intra-anal ointment for the cessation of bleeding and other symptoms associated with internal HD.

Methods: This randomized, double-blind, placebo-controlled study was conducted at 5 sites in Germany. Outpatients with Goligher grade I, II, and/or III hemorrhoids and bleeding were randomly assigned to receive iferanserin ointment 10 mg or inactive vehicle (placebo) BID for 14 days. During treatment, patients rated the severity of HD symptoms daily on a 10-point scale using a diary form. At enrollment and study end, physicians recorded the frequency and intensity of HD symptoms, adverse events, and results from blood and urine analyses on clinical-report forms.

Results: Of the 121 patients enrolled in the study, 118 were evaluable for tolerability and 111 for efficacy. The mean age of the tolerability population was 52.7 years, 78.9% were male, and all were white. The 2 groups had similar HD symptoms at baseline, but overall, patients in the placebo group had numerically higher grades of HD than did patients in the iferanserin group. Compared with placebo, iferanserin was associated with significantly lower patient-reported severity ratings of daily bleeding and itching, beginning at day 1 for bleeding and at day 2 for itching ($P < 0.05$), but not with reduced ratings for severity of other HD symptoms, including pain, tenderness, difficulty with defecation, fullness, throbbing, and gas. In the physician assessments, iferanserin was associated with significantly reduced bleeding frequency by day 14 compared with placebo ($P < 0.05$). Adverse events were mild and infrequent, with no significant differences in prevalences between the 2 treatment groups and no clinically significant changes in laboratory values in any patient.

Conclusion: Compared with placebo, intra-anal iferanserin was associated with significantly reduced patient-reported severity of bleeding and itching and physician-assessed bleeding frequency in these patients presenting with grade I, II, and/or III internal hemorrhoids and bleeding at 5 sites in Germany. ClinicalTrials.gov identifier: 01483833. (*Clin Ther.* 2012;34:329–340)

Key words: bleeding, hemorrhoids, iferanserin, serotonin receptor antagonist.

INTRODUCTION

Hemorrhoid disease (HD) is common, although the precise prevalence has not been reliably estimated. In the United States in 1990, based on data from the National Center for Health Statistics, the estimated prevalence of HD among adults was 4.4%, peaking between the ages of 45 and 65 years.[1] This figure, however, may be an underestimate because some patients do not seek professional medical care for HD, preferring self-medication.[2] In a general-practice sample in Great Britain 40 years ago, the estimated prevalences of HD were 34.8% among men and 37.2% among women.[3] It is possible that more than half of all people experience HD at some point in life.[4]

The etiology of HD is not fully understood. The anal canal consists of several fibrovascular connective cushions, which together serve as a conformable plug that

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ensures a watertight closure. The degenerative effects of aging may weaken or fragment these supporting tissues, and the repeated effects of straining during defecation and/or of the pressures associated with hard stool, heavy lifting, and/or pregnancy may lead to their descent and prolapse.

Prolapsed cushions have impaired venous return, with blood vessels that become congested, enlarged, and inflamed.[5] It has been suggested that the congestion is caused and maintained by 5-hydroxytryptamine (5-HT) (serotonin) release, which by acting on 5-HT_{2a} receptors in the vasculature promotes efferent venous constriction, platelet aggregation, and a cascade effect producing thrombus formation.[6,7] As hemorrhoids worsen, trapped blood forms piles (protruding skin folds filled with static and thrombosed blood) above the pectinate line (internal hemorrhoids) and then below it (external hemorrhoids).

Bleeding—often painless and bright red in color—is one of the most frequent complaints of HD (the Greek root of *hemorrhoid* means "blood flow"). Bleeding occurs as a result of erosion or trauma of the mucosal lining or inflammation damaging the underlying blood vessels. Bleeding has been reported to be the HD symptom that primarily motivates patients to seek a physician's consultation.[8,9] Other common HD symptoms are itching and pain[10]; 5-HT release may lead to those symptoms.[11,12]

Iferanserin is a selective 5-HT receptor antagonist with an affinity for 5-HT_{2a} receptors. It has been hypothesized that an intra-anal ointment application of iferanserin might modify the vascular effects occurring in HD and thereby reduce or eliminate the most frequently occurring symptoms of HD. The goal of the present study was to evaluate the efficacy and tolerability of twice-daily iferanserin intra-anal ointment versus inactive vehicle (placebo) in the cessation of bleeding and other symptoms associated with HD.

PATIENTS AND METHODS

This Phase IIb, 14-day, prospective, randomized, double-blind, placebo-controlled trial of the effects of intra-anal iferanserin was conducted at 5 investigative sites in Germany between September 2001 and August 2002. The trial protocol was approved by the ethics committee of the Chamber of Physicians of Baden-Württemberg (Stuttgart, Germany). All patients provided written informed consent before screening.

Inclusion and Exclusion Criteria

Consecutive ambulatory outpatients aged ≥18 years with a diagnosis of grade I, II, or III hemorrhoids, based on the Goligher classification,[13] and who had at least 1 bleeding episode at least every other day during the 2 weeks before screening, were eligible for enrollment in the study. The Goligher classification assigns a grade to internal hemorrhoids based on the degree of prolapse; such grades are considered useful for helping to guide therapeutic options.[14] In grade I hemorrhoids, tissue protrudes into the lumen of the anal canal but does not prolapse; in grade II hemorrhoids, tissue prolapses but reduces spontaneously; in grade III hemorrhoids, tissue prolapses and requires manual reduction; and in grade IV hemorrhoids, tissue prolapses but cannot be manually reduced.[2] Patients with grade IV hemorrhoids; any large bowel and/or anal canal disease; diabetes mellitus; severe hepatic, renal, and/or cardiovascular disease; any infectious disease; any diagnosis of cancer; and/or pregnancy were excluded.

Study Design

At screening, a complete physical examination and laboratory evaluation were conducted. Randomization at a ratio of 1:1 was achieved by means of opaque sealed envelopes containing assignment to the iferanserin or placebo group.[15] The envelopes were shuffled to produce a random sequence, and each envelope was bundled with an identical package of iferanserin or placebo. The envelopes and packages were dispensed to patients as they qualified for the study. Each package carried a peel label with a coded identification number; for each patient, the investigator affixed the label from the package onto the clinical-report form provided specifically for the study. Investigators and patients were blinded to treatment group assignments and to the contents of the packages.

The ointments were supplied to patients in single-dose, disposable tubes, with each patient receiving 30 separate single-dose units. Patients were instructed to apply the ointment intra-anally BID for 14 days by cleaning the area around the application site, squeezing the contents of the tube directly into the anal canal until emptied, and spreading any remaining ointment around the anus outside of the canal. There were no additional instructions provided to patients regarding the ointment after application. On day 15, after 14 days of treatment, patients were required to return to the investigative sites for another physical and labora-