Preventing Recurrent Venous Thromboembolism with Low-Dose Aspirin

Unprovoked venous thromboembolism (VTE) warrants anticoagulant therapy for a brief period of weeks to months. After it is discontinued, the risk of recurrent VTE remains high. Long-term warfarin therapy is highly effective in preventing recurrence, but it has an increased risk of bleeding, and the monitoring requirements make it inconvenient and costly for patients. Low-dose aspirin is a proposed alternative that is both inexpensive and convenient for patients.

A large multicenter, randomized, double-blind, placebo-controlled study (ASPIRE) evaluated the use of low-dose aspirin to prevent recurrent VTE. The study enrolled patients who had an unprovoked deep-vein thrombosis (DVT) or acute pulmonary embolism (PE) and who were discontinuing anticoagulant therapy. Patients had received between 6 weeks and 24 months of anticoagulant therapy with warfarin or an alternative agent and did not have an indication for continuing anticoagulant therapy. A total of 822 patients were randomly assigned to receive either 100 mg aspirin daily or identical placebo for at least two years and no longer than four years. The primary endpoint was the recurrence of VTE, and secondary endpoints were the incidences of major vascular events (VTE, myocardial infarction, stroke, or cardiovascular death) and clinically relevant bleeding requiring discontinuation of study drug for >14 days. Due to slow recruitment and to strengthen the results, the authors pooled the data with a similar study (WARFASA). Both studies had the same treatments, inclusion and exclusion criteria, and primary endpoint.

In the ASPIRE study, there were fewer recurrent VTEs in the aspirin group compared to the placebo group (18% vs. 14%, respectively; p=0.01). Clinically relevant bleeding rates were similar between the treatment groups (1.9% vs. 3.4%, respectively, p=0.22). In the pooled ASPIRE and WARFASA results, both VTE recurrence and incidence of major vascular events were significantly decreased with aspirin when compared to placebo (19% vs. 14%, respectively for VTE recurrence, p=0.007; 22% vs. 16%, respectively for major vascular events, p=0.002). Clinically relevant bleeding rates did not differ between the groups (2.0% vs. 2.9%, p=0.31). The authors concluded that low-dose aspirin prevented major vascular events in patients who had an unprovoked VTE according to ASPIRE results alone and that the pooled results of ASPIRE and WARFASA showed that low-dose aspirin prevented recurrent VTE. Limitations of this study are the small number of patients due to slow recruitment and the inability to control confounders such as study population differences and comorbid disease states between the two studies in the pooled results.

CONCLUSION: Low-dose aspirin is an inexpensive and convenient treatment option to prevent recurrent VTE and major vascular events for patients who had an unprovoked VTE and are discontinuing anticoagulant therapy.


By Christina Buchman, Pharm.D. Candidate
Rifaximin for the Treatment of Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a common GI disorder characterized by recurrent symptoms of abdominal pain, cramping, discomfort, and inconsistent bowel function. Recent evidence has shown that rifaximin, an antibiotic used in the treatment of traveler’s diarrhea and hepatic encephalopathy, has promise in the treatment of IBS. Rifaximin exhibits a low systemic bioavailability (0.4% after oral administration), minimal side effects, and activity against both gram-positive and gram-negative aerobic and anaerobic bacteria. Some experts believe that the difference in gut flora commonly found between patients with and without IBS may cause the symptoms associated with IBS. Rifaximin alters gut flora, possibly leading to the reduction or resolution of IBS. Currently, rifaximin is not FDA-approved for the treatment of IBS, but phase III trials have shown rifaximin is effective in the treatment of IBS and suggest this drug is equal in efficacy to approved treatments.1,3

A meta-analysis compared rifaximin to placebo in the treatment of IBS.2 Researchers analyzed 5 double-blind, randomized, placebo-controlled trials (N=1,803) examining treatment with 10-14 days of rifaximin (800 mg daily to 1650 mg daily). The primary endpoint of improvement in global IBS symptoms and the secondary endpoint of relief from IBS-related bloating were analyzed. Global IBS symptoms were significantly improved over placebo in the 5 studies (OR=1.57, 95% CI=1.22-2.01, p<0.001; number needed to treat [NNT]=10.2). Increased mean age was an independent predictor in the improvement of global IBS symptoms (OR=1.16, 95% CI=1.07-1.25). IBS-related bloating also improved in the rifaximin group compared to placebo (OR=1.55, 95% CI=1.23-1.96; p<0.001; NNT=10.1). Adverse effects were comparable between rifaximin and placebo. Common events included headache, upper respiratory infection, nausea, nasopharyngitis, diarrhea, and abdominal pain. The authors concluded that rifaximin was effective in the short-term treatment of IBS. They also concluded that rifaximin had similar efficacy as other treatments of IBS (e.g. tegaserod, lubiprostone, alosetron, and diet), based on NNTs from previous studies. The power of the study was limited because only 5 of the 18 studies found met criteria and were analyzed.3

Another trial evaluated rifaximin in patients with IBS and positive lactose hydrogen breath tests.4 A positive LHBT test may indicate rapid small bowel transit and/or small intestinal bacterial overgrowth and is strongly correlated with the positive diagnosis of IBS.4 This phase 4, open-label trial examined the use of 800 mg rifaximin daily for 2 weeks in 106 patients with a positive LHBT test.3 Endpoints, including bloating, diarrhea, flatulence, abdominal pain, and overall well-being, were assessed through a subjective questionnaire rated on a scale of 0-11 (higher scores indicate increased severity). Questionnaires were filled out at baseline and at weeks 4 and 14 after the initiation of treatment. At week 4, a significant number of patients reported decreased severity of bloating (p<0.001), diarrhea (p=0.005), flatulence (p=0.015), abdominal pain (p<0.001) and overall well being (p<0.001). These results were durable at week 14, with the treatment group experiencing significantly less bloating (p<0.001), diarrhea (p=0.008), flatulence (p=0.006), and abdominal pain (p<0.001) and improved overall well-being (p<0.001) compared to baseline. At the end of week 4, 86% of the patients had a negative LHBT test, supporting the link between the test and IBS. The authors concluded that rifaximin was efficacious in improving both the short- and long-term symptoms associated with IBS. They also concluded that a high prevalence of patients with IBS have positive LHBT tests. The major limitation of this study was that the manufacturer of rifaximin funded the study.3 Other limitations included the lack of blinding, randomization, and a control group, which can diminish the validity of the study.3,4

Several studies have shown that rifaximin is effective for treatment of IBS. The novel approach of targeting the flora of the GI tract as a causative agent shows promise for future treatment of this disorder. Rifaximin’s therapeutic benefits were similar to those seen with other treatments (e.g. tegaserod, lubiprostone, alosetron, and diet). Further studies are needed comparing rifaximin to these treatments before recommending this drug as a treatment option for IBS. Rifaximin may be a reasonable alternative for IBS treatment in case of treatment failure with other available agents.

By Anthony Peterson, Pharm.D. Candidate

References:
The True Association between Zinc, Leptin, and Weight Loss: Debunking the Claims of Dr. Oz

Doctor Oz has claimed on television and on his web site that zinc is a new “miracle” weight loss drug that reduces the feeling of hunger by increasing leptin levels.1 Doctor Oz did not share the source that prompted his recommendation, and current evidence from clinical studies of zinc supplementation in humans does not support his assertion that zinc causes weight loss.2,4

It had been proposed that zinc supplementation could increase serum leptin levels in obese patients, leading to decreased hunger and weight loss.2,3 Leptin is a hormone produced by fat cells which signals the brain to regulate appetite, energy expenditure, and fat deposition in the body.4 Current evidence has found that most obese individuals have high circulating leptin levels and are leptin resistant.4 Leptin resistance is similar to insulin resistance: the body produces a sufficient amount of leptin, but the hypothalamus is unable to recognize the signals, which leads to overeating and weight gain.4 It was hypothesized that increasing leptin levels with zinc supplementation would overcome some of the resistance and signal satiety and decrease weight.4 Some studies have evaluated the effects of zinc supplementation on leptin levels and weight loss.2,3

A prospective, randomized, double-blind, placebo-controlled trial was performed to evaluate the effect of zinc supplementation on plasma leptin levels, insulin resistance, body mass index (BMI), and weight after four weeks.2 Women were eligible for the study if they were between 25-45 years old, obese, non-diabetic, and not taking any vitamins. Fifty-six women were randomized to receive either placebo or 30 mg zinc daily for four weeks. Efficiency of zinc supplementation was evaluated by analyzing blood and urine samples and body composition at the start of treatment and after four weeks. Primary endpoints of the study were changes in leptin levels and markers of insulin resistance. Secondary endpoints were the change in BMI, weight, and insulin levels. Leptin levels were similar in both groups at baseline and at the end of the study (p>0.05 for all comparisons). Insulin resistance was significantly improved in the zinc group throughout the study (p<0.05) but not in the placebo group (p>0.05). Weight was relatively unchanged in both groups at the end of treatment with an average of 0.3 kg weight loss in both groups (p>0.05). BMI did not significantly change in either group with a 0.2 kg/m² decrease in the zinc group and 0.1 kg/m² decrease in the placebo group at the end of the study (p>0.05). Circulating insulin levels significantly decreased in the zinc group (p<0.05) but not in the placebo group (p>0.05). No adverse events were reported. The authors concluded that zinc may improve insulin resistance but did not seem to have an effect on leptin levels. Limitations of this study include its small patient population from one geographic region in Korea and potential confounders such as diet and activity.1

Doctor Oz claimed that zinc will lead to weight loss, but clinical studies do not support his assertion. The use of zinc is not associated with weight loss and does not increase serum leptin levels, according to these studies. Zinc supplementation should only be recommended for patients with a documented deficiency and not for weight loss.

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References:
Two recent clinical trials have evaluated the efficacy and safety of aclidinium 200 mcg and aclidinium 400 mcg inhaled twice daily versus placebo for the treatment of COPD. Both studies were randomized, double-blind, placebo-controlled, multicenter trials. Patients were ≥40 years of age, were current or former smokers with a ≥10 pack-year smoking history, and had a forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC) ratio <70% and a FEV₁ <80%. Patients were excluded if they had other significant respiratory conditions, an acute respiratory infection, or a recent COPD exacerbation. Patients were allowed to continue other medications for COPD if their therapy had been stable for four weeks or more prior to enrollment. The primary endpoint for these trials was the change in trough (morning pre-dose) FEV₁ at week 12 and week 24.

The first trial randomized patients to receive aclidinium 200 mcg (n=185), aclidinium 400 mcg (n=190), or placebo (n=186) inhaled twice daily for 12 weeks. The change in trough FEV₁ increased significantly more than in the placebo group (aclidinium 200 mcg: 86 mL, aclidinium 400 mcg: 124 mL, p <0.0001 for both strengths) at 12 weeks. A significant change over placebo (200 mcg: 146 mL, 400 mcg: 192 mL, p <0.0001 both strengths) was also seen in peak FEV₁ (highest value observed within three hours after the morning dose).

In the second study of 828 patients, significant improvements in trough FEV₁ occurred with aclidinium treatment versus placebo. At 24 weeks, aclidinium 200 mcg and aclidinium 400 mcg inhaled twice daily increased mean trough FEV₁ (p ≤0.0001 for both). Mean change from baseline in peak FEV₁ was also significant when compared to placebo (p <0.0001 for both). In addition, there was a significant percent of patients with a clinically significant increase (four or more points) in health status, measured by the St George’s Respiratory Questionnaire (OR 1.47 and OR 1.68, p< 0.001 for both). Adverse drug reactions similar between both treatment groups and placebo in both studies.

Both trials also had better outcomes with the 400 mcg dose compared to the 200 mcg dose. A limitation of both trials is that aclidinium was compared only to placebo and not to the current treatments for long-term maintenance of bronchodilator in patients with COPD.

A Phase IIb, randomized, double-blind, double-dummy, cross-over trial compared aclidinium 400 mcg twice daily to both tiotropium 18 mcg once daily in the morning and placebo. The study consisted of three 15-day treatment periods, separated by a 9- to 15-day washout period, and a follow-up visit. Thirty patients were randomized and 27 completed the study. Inclusion and exclusion criteria were the same as in the trials discussed above. The primary endpoint was the mean change from baseline in FEV₁/AUC₀-12h (area under the curve where the numbers represent the time period for which data were collected divided by the number of hours over which the data are averaged [eg, 0-12 h post-dose divided by 12 h]) at day 15. Aclidinium was significantly better than placebo (difference 221 mL, 95% CI 136 -306 mL; p=0.0001), and no significant differences were found between aclidinium and tiotropium. The authors concluded that aclidinium 400 mcg was safe and well tolerated and its efficacy was similar to once daily tiotropium 18 mcg.

The above trials suggest that aclidinium is a good alternative to Spiriva®. The outcomes in change in FEV₁ appear to be similar to tiotropium, and the safety profile suggests a low incidence of adverse drug events with the use of aclidinium. Tudorza™ Pressair™ may be easier to use than Spiriva®, but it is dosed twice daily versus once daily for Spiriva®. Therefore, the choice between which antimuscarinic to use should be based on patient factors such as compliance and ease of use.

By Christina Anderson, Pharm.D. Candidate

References:
Literature Highlight:
Prophylactic Probiotics to Prevent Death and Nosocomial Infection in Preterm Infants

Preterm infants have a high susceptibility to nosocomial infections (NI) due to their immature immune systems as well as a high rate of exposure to various pathogens while in the neonatal intensive care unit (NICU). In addition, infants are born with a sterile gastro-intestinal (GI) tract; they lack the protective bacteria that reside in the GI tracts of older humans. Lactobacillus reuteri is a well-studied, gram positive bacterium with evidence to support its immunomodulation and bactericidal properties when part of the normal flora colonizing the GI tract. It has been hypothesized that giving infants probiotics in the first hours of their life will make it more difficult for pathogenic bacteria to colonize the GI tracts of these vulnerable infants. A multicenter, double-blind, randomized, placebo-controlled study was conducted to assess if administration of L. reuteri decreased the risk of developing a nosocomial infection of any etiology or death in preterm, low weight infants hospitalized in the NICU.

Eligible preterm infants, less than 48 hours of age, were randomly assigned to treatment with probiotic (10^8 colony-forming units L. reuteri) or placebo drops. Infants were ≤2000 g, hemodynamically stable, and admitted to the NICU. A total of 750 infants were enrolled to receive probiotic (n=372) or placebo (n=378) once daily until discharge or the primary endpoint of either nosocomial infection (NI) or death occurred. The risk of the individual endpoints, NI or death, was similar between the two groups (death: RR 0.8, 95% CI 0.47-1.37; NI: RR 0.88, 95% CI 0.61-1.28). When combined, the risk of the primary endpoints was also similar in each group (RR= 0.87, 95%CI 0.63-1.19; p=0.376).

In addition to NI and death, preterm infants tend to have long hospitalizations, putting them at greater risk of NI, and they may suffer from feeding intolerance. Probiotics may have a role in decreasing these problems; therefore, secondary endpoints of this study included feeding intolerance and duration of hospitalization. When the total population was considered, there was no difference between the groups in the secondary endpoints (feeding intolerance: probiotics n=26, placebo n=40, p=0.08; duration of hospitalization: both groups n=20 days, p= 0.53). However, in infants ≤1500 g, the difference significantly favored probiotics (feeding intolerance: probiotics n=17, placebo n=31, p=0.04; duration of hospitalization: probiotics n=32.5 days, placebo n=37 days, p= 0.03). No adverse drug events were reported for either group throughout the study.

The authors concluded that L. reuteri did not reduce the rate of death or NI; however, they believed the data suggested a protective role. There were many limitations to this study. There might have not been enough patients enrolled to detect a difference between the two groups. In addition, other medications or treatments the infants were receiving were not discussed in this study, and the patients were allowed different forms of nutrition (mother’s milk, cow-based formula, mother’s milk plus formula), which could confound the results of the data. Generalization of this study is limited since it was only conducted in major metropolitan centers in Colombia. The results of this study may have been different if it had been conducted in rural areas or other countries, due to resources available or different standards of care.

Conclusion: The use of L. reuteri in preterm infants hospitalized in the NICU did not decrease NI or death. However, the use of probiotics may be beneficial in reducing feeding intolerance and duration of hospitalization among the very low weight (≤ 1500 g) preterm infants.


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