



## Health Matters May 2009; Volume 3, Issue 7

# Proton pump inhibitors and Plavix: Cause for concern?

Clopidogrel, which prevents arterial thrombosis by inhibiting platelet activation, is commonly prescribed after acute coronary syndromes and stent implantation. Because clopidogrel may also increase the risk of bleeding, a proton pump inhibitor (PPI) is frequently given concurrently to decrease the risk of gastrointestinal bleeding. However, recent reports suggest that PPIs, and specifically omeprazole, may interfere with the antiplatelet effect of clopidogrel.<sup>1</sup>

Clopidogrel is a prodrug that is activated by CYP450 enzymes in the liver, predominately CYP2C19. All PPIs are thought to inhibit CYP2C19 to some extent, with omeprazole (Prilosec™) being a strong inhibitor of this isoenzyme. This mechanism of action forms the basis for the suspected interaction, which is thought to involve reducing platelet reactivity and therefore increasing cardiovascular risk. Pantoprazole (Protonix™) has less effect on CYP2C19, and therefore is thought to be less likely to interact with clopidogrel.<sup>1</sup>



A retrospective review of pharmacy claims data assessing patients taking concomitant clopidogrel and PPI therapy was published by Pezella and colleagues.<sup>2</sup> Approximately 1000 patients were divided into 2 groups: those with low exposure (PPI therapy for less than 6 months) and those with high exposure (PPI therapy for greater than 6 months). Patients taking clopidogrel without PPI therapy were the control group. Adjusted results showed a statistically significant difference in one-year myocardial infarction rates between the control group and high exposure group. ( $p < 0.05$ )

A randomized, double blind, placebo-controlled trial of 140 coronary stent patients taking clopidogrel in combination with a PPI was published by Gilard and colleagues in 2008. The study was designed to assess platelet reactivity, measured and reported as the platelet reactivity index (PRI). The PRI is inversely related to the effectiveness of platelet activation reduction, suggesting a higher PRI is associated with a poor response to clopidogrel therapy. All patients received aspirin and clopidogrel therapy, and were randomized to receive either omeprazole 20 mg daily or placebo for seven days. Prior to entry into the study, there was no statistical difference in mean PRI between the two groups. On day seven, the placebo group had a statistically lower PRI than the omeprazole group. (39.8% vs 51.4%;  $p < 0.001$ ). This data suggested clinical concern about an interaction between clopidogrel and PPIs, and was the basis for further study of this issue.<sup>3</sup>

Juurink et al. performed a case-control study of 734 clopidogrel patients who were either readmitted with a diagnosis of myocardial infarction, or died within 90 days of hospital discharge post-myocardial infarction.<sup>4</sup> Patients were matched with 2057 controls based on age, intervention, date of discharge and predicted mortality probability. Patients in the study received a prescription for clopidogrel within three days of discharge from the hospital following treatment for acute myocardial infarction, and were followed for 90 days post-discharge or until readmission. Use of PPIs (omeprazole, lansoprazole, rabeprazole or pantoprazole) was associated with an increased risk of reinfarction. (OR 1.27, 95% CI 1.03-1.57). Individual assessment of the PPIs did not show an association between pantoprazole and recurrent myocardial infarction. It is theorized that this lack of association may be due to the minimal effect of pantoprazole on the CYP2C19 isoenzyme.

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## PPIs and Plavix, continued from page 1

In March 2009, Ho and colleagues published a retrospective cohort study of more than 8200 acute coronary syndrome (ACS) patients discharged on clopidogrel from VA hospitals.<sup>5</sup> Approximately 64% of these patients were also prescribed a PPI upon discharge: 60% omeprazole; 3% rabeprazole; < 1% lansoprazole or pantoprazole; 36% more than one type of PPI. The primary outcome was the combined end point of all-cause mortality or rehospitalization for ACS. Rates of death or rehospitalization were significantly greater for the clopidogrel and PPI patients than for those patients not taking a PPI. (29.8% vs 20.8%; Adjusted OR=1.25; 95% CI=1.11-1.41) Secondary outcomes analyses showed significantly higher risks in patients taking PPIs in conjunction with clopidogrel for rehospitalization and revascularization episodes. Patients taking PPIs without clopidogrel following discharge from the hospital did not experience any increased risk of death or rehospitalization.

Although data is preliminary, there is evidence to suggest that there is the potential for an interaction between clopidogrel and PPIs, which results in decreased antiplatelet effects. The theorized mechanism behind this interaction is inhibition of the CYP2C19 isoenzyme; however, this has not been proven. Omeprazole is one of the most potent inhibitors of CYP2C19, and current evidence suggests it has demonstrated the strongest association with clopidogrel. Pantoprazole is the least likely PPI to inhibit CYP2C19, and there is limited evidence suggesting lack of an association between pantoprazole and an increased risk of cardiovascular events in this situation. Although further study is needed to clarify the potential for this interaction, pantoprazole may be the most prudent choice for use in combination with clopidogrel at this time.

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## Do DHA-supplemented infant formulas provide any benefits? by Jacqueline G. Mercado

There are several different types of baby formula available on the market. Each must meet the Food and Drug Administration's (FDA) requirements, including minimum amounts of various nutrients.<sup>1</sup> In 2002 new additives were considered safe for term infant formulas and were approved by the FDA. These are extra long-chain polyunsaturated fatty acids (LCPUFA), namely arachidonic acid (ARA or AA) and docosahexaenoic acid (DHA)<sup>2</sup> which are both found in human breast milk. These LCPUFA are important components of membrane phospholipids and play an important role in brain cell and retinal function.<sup>3</sup> Adding LCPUFA to infant formulas was intended to mimic the natural amounts found in human milk because breastfed infants typically have higher blood levels of DHA and ARA than infants fed formulas without these additives.



In theory, the addition of DHA & ARA should provide benefits similar to breastfeeding, with improved visual and cognitive function when compared to infants fed formula without these fatty acids.<sup>4</sup> However, the benefits of DHA-supplemented infant formulas are still to be proven. This is especially important when considering how much more expensive the enhanced formulas are when compared to the standard formulas currently available.

## DHA-supplemented formula, continued on page 3

## DHA-supplemented formula, continued from page 2

An Australian study compared the effects of high dose DHA (1%) with the standard DHA concentration (~3%) in preterm infants. DHA 1% concentration is comparable to the level a fetus is exposed to during intrauterine development. The participants in this study were from one institution and the infants represented a wide range of gestational ages and medical comorbidities that are commonly seen in preterm infants. Mothers of all infants were encouraged to first breast feed and then supplement with formula when needed, which is what is typically promoted in most neonatal units. DHA concentration in breast milk was manipulated to high-dose by giving mothers oral supplementation of tuna oil, or to the standard by giving them placebo capsules. In this single-center, double-blind, randomized, controlled trial, they found that the infants in the high-dose DHA group had a significantly higher visual acuity at 4 months corrected age (CA), compared to the infants in the control group. ( $P=0.025$ )<sup>5</sup>

Another study compared DHA supplemented and non-DHA supplemented formula groups who were given study formula (0.32% DHA, 0.30% ARA or no DHA or ARA) for 6 months. A non-randomized breastfed reference group was also included. At 4-6 years of age, the breastfed children had a mean stereoacuity that was statistically higher than the formula fed groups ( $P=0.002$ ). The difference between the two formula groups did not differ significantly ( $P=0.9$ ). These statistics remained the same even after including potential confounding factors such as socioeconomic status, maternal and demographic characteristics.<sup>6</sup>

In a single-center, double-blind, randomized clinical trial, visual and cognitive outcomes of DHA- and ARA- supplemented formulas were evaluated at 4 years of age. One arm consisted of formula-fed infants for the first 17 weeks of life. They were randomized to one of three formulas: control, 0.35% DHA supplemented, or 0.36% DHA+ 0.72% ARA supplemented. A non-randomized breastfed group was used as the "gold standard" and were breastfed for an average of 43 weeks. At 4 years of age, the control formula-fed group had significantly poorer visual acuity in the right eye than breastfed children ( $P<0.004$ ) and the DHA supplemented group ( $P<0.03$ ). The breastfed group also had significantly higher Verbal IQ scores than both the control formula group and DHA groups ( $P<0.02$ ).<sup>7</sup>

In a multi-centered, double-blind, randomized, parallel group control trial, growth was assessed for the first 120 days of age with and without DHA or ARA supplementation of soy-based formula. At 30 and 90 days of age, the mean achieved weight was significantly higher in the control group than the treatment group ( $P<0.05$ ). However, the control group was also heavier and longer at baseline. Although there were no significant differences in rate of weight gain between the two groups throughout the study, the authors claim that supplementation of DHA+ARA supports normal growth since the differences in growth were consistent between the two groups from baseline to the end of the 4 month study.<sup>8</sup>

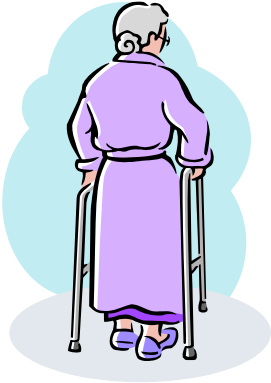
A study in Spain found that infant formulas supplemented with DHA+ARA in concentrations similar to human breast milk may reduce the incidence of bronchitis in the first year of life. This multi-center, prospective, open-label, observational study included healthy term infants from across the country. Depending on the pediatrician's normal practice, participants received one of the following: 1) DHA+ARA-supplemented formula, 2) low-concentrations of DHA and ARA or 3) no supplementation. At 5, 7 and 9 months old, the control group had a significantly higher incidence of bronchitis ( $P=0.0001$ ,  $P=0.01$ ,  $P=0.01$ , respectively). The incidence of upper airway infection was also significantly higher in the control group at 1 month and 12 months ( $P=0.05$ ,  $P=0.01$ , respectively).<sup>9</sup>

The American Academy of Family Physicians recommends breastfeeding as the standard of care for infant nutrition for the first 6 months of life followed with the incorporation of other foods and human milk for the next 6 months. Controlled clinical trials done in the past three years have not shown DHA supplementation at standard concentrations to be superior to human milk or non-supplemented formulas in terms of improving visual acuity or other benefits in the long term. However, higher concentrations of DHA may benefit visual acuity in preterm infants, suggesting that an optimal dose has yet to be determined.

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## Loop Diuretic Use & Fractures in Postmenopausal Women by Ashley Pham



Osteoporosis remains a major concern for increasing the risk of fractures, especially in postmenopausal women. Loop diuretics may also be associated with low bone mineral density (BMD) which increases the risk for fractures, as well as orthostatic hypotension, which increases the risk for falls.

An article recently published in the Archives of Internal Medicine reported on the Women's Health Initiative (WHI) prospective study. Subjects included women between 50 and 70 years of age who were enrolled in the WHI observational study and clinical trials from October 23, 1993 to December 31, 1998, and who were not in the active arms of the hormone or calcium and vitamin D trials. The study population included 3,411 loop diuretic users and 130,444 nonusers. Questionnaires were used to gather demographic information, medical histories, and data on dietary intake of calcium and vitamin D. Study participants were asked to bring in the medication bottles for any drugs taken during the two weeks prior to the baseline visit and the year-3 visit. At 3 of the 40 WHI clinical centers, BMD of the total hip, anterior-posterior lumbar spine, and total body was measured at baseline and at year-3. Total fractures were defined in the WHI clinical trials as "all clinical fractures excluding those of the ribs, sternum, skull or face, fingers, toes and cervical vertebrae." A history of falls was characterized as "2 or more reported falls in the year prior to baseline."

The results of this study revealed that there was no significant association between the ever use of loop diuretics and changes in BMD, falls, or fractures in postmenopausal women enrolled in the WHI. There was, however, a small increased risk of total fractures (HR= 1.16, 95% CI, 1.03-1.31) and clinical fractures excluding hip, vertebral, and lower arm/wrist fractures (HR=1.16, 95% CI, 1.01-1.33) in women using loop diuretics for more than 3 years. The investigators did not find a significant association between loop diuretic use and changes in BMD from baseline to year 3.

Although there was a slight increased risk of total and other clinical fractures in patients with prolonged use of loop diuretics, the results are not enough to warrant any changes in practice recommendations at this time. The lack of sufficient evidence from this study suggests that more research is needed regarding any possible association between patients taking loop diuretics and incidence of fractures.

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## First Topical Therapy for Overactive Bladder by Arshdeep Pooni

In January of 2009 the U.S. Food and Drug Administration (FDA) approved Gelnique® (oxybutynin chloride) Gel 10%, the first topical gel for the treatment of overactive bladder. Oxybutynin, an antimuscarinic agent, was originally approved for use in 1975 as oral therapy for overactive bladder. It is also available as a transdermal patch and an oral tablet.<sup>1</sup>

Gelnique® is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. Gelnique® is a muscle relaxant and works by suppressing the urge to void by inhibiting involuntary detrusor muscle contractions caused by detrusor muscle instability or detrusor muscle hyperreflexia. This reduction in contractions allows the bladder to relax and increases its visceral capacity. Consequently urgency is decreased by delaying the initial desire to void.<sup>2</sup> Gelnique® is a non-selective antimuscarinic, therefore the most common side effect reported was dry mouth. Concomitant use of Gelnique® with other anticholinergic agents may increase the frequency of anticholinergic pharmacological effects. Application site reactions were another common side effect (incidence >5% and >placebo).

A 12 week, randomized, double-blind, placebo-controlled, parallel group study was conducted to evaluate the safety and efficacy of Gelnique®. A total of 789 patients were randomized, with 389 patients in the treatment group and 400 patients in the placebo group. The majority of the patients, 89%, were women and the mean age was 59 years. The key inclusion criteria in the study were adults with symptomatic overactive bladder with four or more incontinence episodes in a 3-day period and at least eight micturations per day. Patients in the treatment arm received 1 gram of Gelnique® daily and patients in the placebo arm received a matching placebo daily for 12 weeks. The results indicated a more significant decrease in the mean number of urge incontinence episodes in patients treated with Gelnique® than in the placebo group (-3.0 vs -2.5 per day,  $p < 0.0001$ ). Mean urinary frequency (-2.7 vs -2.0 per day,  $p = 0.0017$ ) was lower in the treatment group compared to the placebo group. Additionally, voided volume was increased in the treatment group over the placebo group (21.0 ml treatment, 3.8 ml placebo,  $p = 0.0018$ ). Treatment related dry mouth was seen more frequently in the treatment group versus the placebo group (6.9% and 2.8% respectively). Application site reactions were infrequent but appeared in a higher percentage of the treatment group patients (5.4% vs 1.0%). The study did not report any serious treatment related side effects.<sup>3</sup>

Gelnique® is absorbed through the skin and it crosses into the systemic circulation by passive diffusion across the stratum corneum. The drug achieves steady state concentrations after 7 days of continuous dosing.<sup>1</sup>

An advantage of Gelnique® over oral therapy of oxybutynin is the lack of first-pass gastrointestinal and hepatic metabolism. Oral therapy would involve possible interactions between oxybutynin and other drugs metabolized by P450 enzymes, particularly CYP3A4.<sup>2</sup> This lack of interactions may give Gelnique® an enhanced safety profile over oral therapy however at this time there are no head-to-head trials involving Gelnique® and oral therapy or Gelnique® and the transdermal patch.

The dose of Gelnique® is 1 gram (one sachet) applied once daily to dry, intact skin on the abdomen, upper arms/shoulders, or thighs. Concomitant application of sunscreen, either before or after Gelnique® application had no effect on the systemic exposure of the drug. Additionally, showering one hour after application had no effect on overall systemic exposure.<sup>1</sup>

Gelnique® is supplied as unit dose sachets that contain 1 gram (1.14 ml) of the gel. It is expected reach the market later this year. Pricing information is not available at this time.

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