Clinical Pharmacy Newsletter

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INSIDE THISISSUE:

New Studies Support Dropping Long-term Aspirin after Stenting

Two new studies from Asia provide more evidence that extended monotherapy with clopidogrel or another P2Y12 inhibitor antiplatelet, rather than either dual antiplatelet therapy with aspirin plus a P2Y12 inhibitor or aspirin alone, may be the preferred strategy after placement of a drug-eluting stent in patients with heart disease.In the Japanese STOPDAPT-2 study, 1-month dual antiplatelet therapy followed by clopidogrel monotherapy provided a net clinical benefit with respect to ischemic and bleeding events compared with 12-month dual antiplatelet therapy with aspirin and clopidogrel after implantation of cobalt-chromium everolimus-eluting stents. The benefit was driven by a significant reduction in bleeding events without an increase in ischemic events. And in the Korean SMART-CHOICE study, extended P2Y12 inhibitor monotherapy after 3-month dual antiplatelet therapy was non-inferior to 12-month dual antiplatelet therapy in terms of ischemic events at 12 months, and it was associated with less bleeding.

The trend towards monotherapy with a P2Y12 inhibitor is fascinating, and closer to believe that this may become a definitive therapy. But either of these current trials or even the combination of them both together gives enough evidence to say that this should be current clinical practice at present. However, this is a very important trend, and not be surprised if in the next 3 to 5 years this does become the more standard therapy to use with a broad range of drug-eluting stents. These are two of the largest trials so far of the strategy of replacing long-term aspirin monotherapy with long-term P2Y12 inhibitor monotherapy after a short period of dual antiplatelet therapy.

These studies included intravascular imaging, which is standard practice in Japan and Korea. When this is incorporated into the study, it is often possible to make better decisions about whether to implant a stent and how large the stent should be- and this can lead to lower events rates. This affects the power of the study - both these studies had low event rates - and it can also neutralize the benefits of pharmacotherapy. The thrombotic risk of the patients included in these two studies was lower than would be expected in patients in the United States who undergo stenting. For this reason, the potential ramification of stopping aspirin in a higher-risk population cannot be understood from these data.

Now these two studies together with some previous data suggest that dropping aspirin is potentially a very smart strategy in certain individuals.

STOPDAPT-2: The study included 3009 patients who received a drug-eluting stent at 89 centers in Japan. Of these, 38% had acute coronary syndrome. They were randomly assigned to receive either standard dual antiplatelet therapy for 1 year or dual antiplatelet therapy for the first month followed by clopidogrel alone after that.

The primary endpoint — a composite of cardiovascular death, myocardial infarction (MI), definite stent thrombosis, stroke, or TIMI (thrombolysis in myocardial infarction) major/minor bleeding at 12 months-occurred in 2.4% of the patients who stopped taking aspirin after 1 month compared with 3.7% of those who took dual antiplatelet therapy for the whole year (hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.42 – 0.98; *P* = .04).

The key ischemic endpoint- the rate of cardiovascular death, MI, definite stent thrombosis, and stroke- was similar in the two groups: 2.0% in the group that stopped taking aspirin after 1 month vs 2.5% in those who received dual antiplatelet therapy for a year (HR, 0.79; 95% CI, 0.49 – 1.29).
TIMI major/minor bleeding occurred in 0.4% of those who stopped taking aspirin after 1 month, vs 1.5% of those taking dual antiplatelet therapy for the year (HR, 0.26; 95% CI, 0.11 – 0.64; *P* = .004).

According to the study findings, 1-month dual antiplatelet therapy followed by clopidogrel monotherapy could be a good option after drug-eluting stent implantation with an advantage of fewer bleeding events, the study concluded.

SMARTCHOICE: The trial enrolled 2993 patients who underwent percutaneous coronary intervention (PCI) and received a drug-eluting stent at 33 medical centers in South Korea. They were randomly assigned to receive either standard dual antiplatelet therapy for a year or aspirin plus a P2Y12 inhibitor for 3 months and to continue with only the P2Y12 inhibitor for 9 more months after that.

Of the different P2Y12 inhibitors, 77% of the patients took clopidogrel, and 23% took either Prasugrel (Effient) or Ticagrelor (Brilenta). Results showed that stopping aspirin early was not inferior to dual antiplatelet therapy in terms of preventing ischemic events.

After 1 year, the primary ischemic endpoint — a composite of death from any cause, MI, or stroke — had occurred in 2.9% of patients who stopped taking aspirin, vs 2.5% of those who took standard dual antiplatelet therapy for a year (P = .007 for non-inferiority).In addition, bleeding events were significantly reduced in the group who stopped taking aspirin early. Bleeding (BARC type 2–5) occurred in 2% of the those who stopped taking aspirin at 3 months compared to 3.4% of those who received dual antiplatelet therapy for a whole year (HR, 0.58; 95% CI, 0.36 – 0.92; P = .02).

Taken together, the net rate of all adverse clinical events (death from any cause, MI, stroke, or bleeding) was not significantly different between the two groups.

One limitation of the study is that a considerable proportion of patients in the group assigned to stop taking aspirin early in fact received aspirin after 3 months, although a more detailed analysis suggested that this discrepancy did not undermine the overall findings.

The SMART-CHOICE trial suggests that P2Y12 inhibitor monotherapy after short duration of dual antiplatelet therapy is a novel antiplatelet strategy balancing ischemic and bleeding risk in patients undergoing PCI, the study concluded.

Reference:
https://www.medscape.com/viewarticle/911030

Often Feel Bloated? One Ingredient May Be to Blame

If you often feel bloated after a meal, don't be too quick to blame high-fiber foods. The real culprit might surprise you. Your gut may be rebelling because you're eating too much salt, a new study suggests.

"Sodium reduction is an important dietary intervention to reduce bloating symptoms and could be used to enhance compliance with healthful high-fiber diets," said study researcher Noel Mueller, an assistant professor at the Johns Hopkins Bloomberg School of Public Health in Baltimore. He and his research colleagues looked at data from a large clinical trial conducted in the late 1990s known as Dietary Approaches to Stop Hypertension-Sodium, or DASH-Sodium for short.

Their conclusion: Consuming a lot of salt increases bloating, as does a healthy, high-fiber diet.

Although it's not clear exactly how salt contributes, Mueller suspects fluid retention may be the key. Eating more salt can promote water retention and make digestion less efficient, which can lead to gas and bloating, he said. Studies in mice have shown that dietary salt can alter the makeup of gut bacteria. And that, in turn, can affect gas production in the colon, Mueller said.

"Our study suggests that selecting foods with lower sodium content, such as those that are not ultra-processed, may help relieve bloating in some people," he said.

Bloating affects as many as a third of Americans, including more than 90% of those with irritable bowel syndrome. It's a painful buildup of excess gas created as gut bacteria break down fiber during digestion. For the current study, the researchers used findings from a 1998-1999 trial. In that trial, the DASH diet -- one low in fat and high in fiber, fruits, nuts and veggies -- was compared with a low-fiber eating regimen. The trial's goal was to learn how salt and other factors affected high blood pressure. The new review found that about 41% on the high-fiber diet reported bloating, and men had a bigger problem with it than women. And diets high in salt increased the odds of bloating by 27%."We found that in both diets, reducing sodium intake reduced bloating symptoms," Mueller said. The upshot is that reducing sodium can be an effective way to prevent gas -- and may help people maintain a healthy, high-fiber eating regimen.

Many things can cause bloating -- lactose intolerance, celiac disease, small intestinal bacterial overgrowth, infection or other conditions, said Samantha Heller, a senior clinical nutritionist at New York University Langone Health.

"If someone is experiencing gastrointestinal symptoms such as bloating on an ongoing basis, they should see their health care practitioner to see if the cause can be pinned down," said Heller, who wasn't involved with the study. "This way they will know how to manage the issue."

Occasional bloating is not uncommon, she added. To help you avoid excess gas and bloating, Heller offered these tips:

- Increase physical activity.
- Limit highly processed foods, such as fast food, frozen meals, junk food and fried food.
- Increase your fluid intake, and make peppermint tea part of it. Avoid carbonated beverages.
- Eat more foods that are rich in fiber, such as vegetables, legumes and whole grains. Increase these slowly and in small portions, and be sure to increase your fluid intake at the same time.
- Have smaller meals.

Reference: Peng AW, Juraschek SP, Appel LJ, Miller ER, Mueller NT. Effects of the DASH Diet and Sodium Intake on Bloating: Results From the DASH–Sodium Trial. American Journal of Gastroenterology. 2019 Jul 1;114(7):1109-15.

DRUG PROFILE

TRICLABENDAZOLE

Class: Anthelmintic

Indication: Anthelmintic treatment of Fascioliasis in patients aged 6 years or older.

Mechanism of Action:
The exact mechanism of action by which Triclabendazole exhibits its effect against Fasciola species is not fully elucidated. Studies in-vitro and infected animals suggest that triclabendazole and its active metabolites are absorbed by the tegument of the immature and mature worms, leading to a decrease of the resting membrane potential, inhibition of tubulin function as well as protein and enzyme synthesis. These metabolic disturbances are associated with inhibition of motility, disruption of the surface as well as inhibition of spermatogenesis and vitelline cells.

Dosage form and Administration:
Triclobendazole is available in the form of tablets. Each tablet is of 250 mg strength, pale red, speckled, capsule shaped, biconvex with imprint of "EG EG" on one side and functionally scored on both sides.
The recommended dose of Triclobendazole is 2 doses of 10 mg/kg given 12 hours apart in patients 6 years of age and older. The 250 mg tablets are functionally scored and divisible into two equal halves of 125 mg.
Triclobendazole tablets can be swallowed whole or divided in half and taken with water or crushed and administered with applesauce. The crushed tablet mixed with applesauce is stable for up to 4 hours. Tablets should not be stored above 30°C.

Dosing in Renal & Hepatic Impairment:
Drug should be used with caution in patients with renal or hepatic impairment. No data is available regarding use of Triclobendazole in hepatic and renal impaired patients.

Pharmacokinetics:
Following oral administration of a single dose of triclabendazole at 10 mg/kg with a 560-kcal meal to patients with fascioliasis, the median Tmax for the parent compound and the sulfoxide metabolite was 3 to 4 hours. Cmax and AUC of triclabendazole and sulfoxide metabolite increased approximately 3-fold and 2-fold respectively when triclabendazole was administered as a single dose at 10 mg/kg with a meal.

Apparent volume of distribution of the sulfoxide metabolite is approximately 1 L/kg. Protein-binding of triclabendazole, sulfoxide metabolite and sulfone metabolite in human plasma was 96.7%, 98.4% and 98.8% respectively. The plasma elimination half-life of triclabendazole, the sulfoxide and sulfone metabolites in humans is approximately 8, 14, and 11 hours, respectively. Based on in vitro studies, majority of triclabendazole is primarily metabolized by CYP1A2 (approximately 64%). No excretion data is available in humans. However, in animals, the drug is largely excreted via the biliary tract in the feces (90%), together with the sulfoxide and sulfone metabolite.

Adverse Reactions:
Adverse reactions reported in less than or equal to 2% of patients who received a total of 10 mg/kg of Triclabendazole were constipation, biliary colic, arthralgia, back pain, spinal pain, and chromaturia. Some adverse reactions associated with triclabendazole treatment in fascioliasis, e.g. abdominal pain, biliary colic, and jaundice, could be secondary to the infection and may be more frequent and/or severe in patients with a heavy worm burden.

Liver Enzyme Elevations: In clinical studies, up to one third of patients had liver enzyme elevations at baseline, which generally improved post-treatment. Elevations of AST, ALP and ALT were reported in the patients.

Contraindications:
- Pregnancy: Drug should not be used during pregnancy. No adequate clinical data on exposed pregnancies are available for Triclobendazole.
  Embryo-fetal developmental toxicity studies revealed no malformations in rats and rabbits at doses up to 200 mg/kg/day and 20 mg/kg/day, respectively.
- Drug is contraindicated in patients with history of allergy to triclabendazole or other benzimidazole derivative drugs.

Precautions:
- Transient prolongation of the mean QTc interval was noted on the electrocardiographic recordings in dogs.
- Patients with a history of prolongation of QTc or symptoms of long QT interval should be monitored with ECG during drug use.

Drug Interactions:

- Clinical drug interaction studies have not been conducted for triclabendazole.
- In Vitro Studies Triclabendazole and its sulfoxide and sulfone metabolites have the potential to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A enzymes at clinically relevant plasma concentrations, with the highest potential of inhibition on CYP2C19.

Reference:

- https://www.novartis.com (Novartis Pharmaceutical company Website)
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208711s000lbl.pdf (US FDA Website)

EVENT CORNER

REPORT

Highlights of the Department of Pharmacy Practice:

Dr. K. P. Arun, Asst. Professor, acted as 'Coordinator' and 'Resource person' for the national level Workshop 'Summer School of Ooty on Applied Pharmacokinetics - 2019 (SOAP - 2019)' organized by Department of Pharmacy Practice, JSS College of Pharmacy, Ooty in association with IPA Nilgiris branch, between 8th -13th, April 2019. The workship included a total of 38 participants (31-External participants and 7- Internal participants)

Ms. M. Deepalakshmi, Lecturer acted as 'Staff coordinator' for the national level workship 'Summer School of Ooty on Applied Pharmacokinetics - 2019 (SOAP - 2019)' organized by Department of Pharmacy Practice, JSS College of Pharmacy, Ooty in association with IPA Nilgiris branch between 8th -13th, April 2019.

Dr. Keerthana C, Resident, attended the national level work-shop, 'Summer School of Ooty on Applied Pharmacokinetics - 2019 (SOAP - 2019)' organized by Department of Pharmacy Practice, JSS College of Pharmacy, Ooty in association with IPA Nilgiris branch between 8th -13th, April 2019.

Dr. S Ponnusankar, Professor & Head, Department of Pharmacy Practice, JSS College of Pharmacy, Ooty delivered an Invited talk on the topic 'Clinical Pharmacy Services at the Public Hospital' at National level conference, 'Pharmacy Practice Summit-2019' organized by Chitkara College of Pharmacy, Chitkara University, Punjab between 19th -20th April 2019.

Mr. Vishwas H N acted as 'Staff coordinator' from JSS College of Pharmacy, Ooty for the national level personality development program, 'Retreat for Pharmacy, Dental Ayurveda and Engineering students' Organized by Jagadguru Sri Veerasimhasana Mahasamsthana Math, Sutturu Srikshetra, JSS Mahavidyapeetha, Sri Shivarathreeshwara Endowment Trust, Mysuru at Sutturu Sriskshetra between 9th -11th April 2019.

Dr. K P Arun, Asst. Professor and Dr. Keerthana C, Resident, Department of Pharmacy Practice, JSS College of Pharmacy, Ooty attended a national level workshop on 'Developing a protocol for a systematic review' organized by 'Prof. BV Moses Centre for Research and Training in Evidence Informed Health care' at Christian Medical College, Vellore between 20th - 24th May 2019.

Mr. C. Jayakumar, Asst. Professor, Department of Pharmacy Practice acted as a Resource person and delivered at talk on 'IT tools used in research' at state level workshop on 'Biostatistics, Research Methods, Communications and Ethics' organized by :TIFAC Core-Dept of Pharmacognosy at JSS College of Pharmacy, Ooty between 13th -15th May 2019.

Mr. Vishwas H N, Lecturer, Department of Pharmacy Practice acted as a Resource person and delivered at talk on 'Importance of Communication & Research etiquette' at state level workshop on 'Biostatistics, Research Methods, Communications and Ethics' organized by: TIFAC Core- Dept of Pharmacognosy at JSS College of Pharmacy, Ooty between 13th -15th May 2019.

Ms. Roopa BS, Lecturer, Dept. of Pharmacy Practice got selected as a 'Reviewer' for the Journal 'Current Medicine Research and Practice' of Elsevier Publications on 14th June, 2019.

Dr. S. Ponnusankar and other experts involved in Panel discussion at 'Pharmacy Practice Summit-2019' at Chitkara University, Punjab (19th - 20th April 2019)

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