MEDICAL PHARMACIES TABLET

Drug information and news for health care providers

June 2013

IS ASPIRIN® RESISTANCE A MYTH?

True resistance to Aspirin® (ASA) may be quite rare, according to Dr. Tilo Grosser, the lead author of a study in *Circulation* (doi: 10.1161/CIRCULATIONAHA.112.117283) that evaluated the response of 400 healthy individuals to immediate-release ASA and enteric-coated ASA.

In the first phase of the three-phase study, individuals were screened for their response eight hours after a single oral dose of ASA 325 mg. The 40 participants given immediate-release ASA were all responders (defined as having achieved a reduction in platelet aggregation factor of more than 60%). Of the 210 individuals taking enteric-coated ASA, 17% were deemed nonresponders. The third group of 150 people also took enteric-coated ASA, but their response was measured four hours after dosing. In this group 49% were nonresponders. The authors explained that the response with coated ASA depended on when the test was done, which, of course, makes sense. The pharmacokinetics of enteric-coated ASA is such that absorption is delayed until it reaches the small intestine to minimize gastrointestinal adverse effects. As a result, if measurement of platelet reactivity is taken only a few hours after ingestion of enteric-coated ASA, this would not be unexpected.

The study continued in a second phase where people taking immediate-release ASA were all responders. The third phase of the study consisted of a control group of 25 people from the responder group and 27 people who had not responded in either phase one or phase two of the study. Each group followed the same regimen, namely 81 mg of daily ASA for one week. Only one of the patients in the nonresponder group and two from the control group failed to respond to this regimen. Although the researchers were not able to verify it, they suspected the nonresponders were not compliant.

The researchers concluded that coated Aspirin® will eventually have the desired effect, but it must be taken reliably every day, and the onset of action takes a few days—which is no problem for chronic therapy, but the compliance issue may be.

This study failed to identify a single case of true drug resistance, but the researchers pointed out that pseudoresistance—reflecting delayed and reduced drug absorption—complicates enteric-coated but not immediate-release ASA administration.

Therefore, a patient who is classified as ASA-resistant when tested may actually be noncompliant, or perhaps the testing is done too early in therapy. If ASA doses are increased in these patients, they may be exposed to additional gastrointestinal risk for no additional benefit.

However, Dr. Sanjay Kaul, director of the vascular physiology and thrombosis research laboratory at Cedars-Sinai Medical Center in Los Angeles, cautioned against extrapolating the results to patients with heart disease or chronic illnesses that may affect how ASA works in the body. MPT

HIGH-POTENCY STATINS MAY CAUSE KIDNEY INJURY

High-potency statins are linked to an increase in acute renal toxicity during the first 120 days of therapy compared with low-dose statin regimens, according to an observational analysis published in the *British Medical Journal* (2013;346:f880 doi:10.1136/bmj.f880). The paper retrospectively analyzed databases in Canada, the UK, and the US to examine records of over two million patients aged 40 years and older who took statins for a period exceeding 11 years. They found that in patients with nonchronic kidney disease, current users of high-potency statins were 34% more likely to be hospitalized with acute kidney injury within 120 days of starting treatment. Patients with pre-existing kidney disease showed a smaller (roughly 10%) increase in risk with high-dose treatment. High-potency statins are considered ≥ 10 mg of rosuvastatin (Crestor®), ≥20 mg of atorvastatin (Lipitor®), and ≥ 40 mg of simvastatin (Zocor®). All other statins are considered low potency.

This finding translates into one hospitalization for acute kidney failure for every 1,700 patients treated with a high-dose statin for 120 days. Although previous studies suggested high-dose statins were associated with kidney failure, they tended to be too small to establish a definite link. This study is large enough to strongly support a real risk.

A one in 1,700 risk of kidney toxicity may appear to be a relatively small risk, until one takes into account that statins are widely prescribed, often at high doses and frequently given to relatively young, healthy people. MPT

Apprilon® (doxycycline) 40 mg capsules

Galderma

Apprilon is a low-dose modified-release doxycycline indicated solely for the treatment of inflammatory lesions (papules and pustules) of rosacea in adults. It is not effective in reducing generalized redness of the skin. The capsules contain 2 types of beads: immediate-release beads containing 30 mg of doxycycline and delayed-release beads containing 10 mg of doxycycline. The dual release mechanism does not result in sufficient blood levels of doxycycline to treat bacterial infections or provide antibacterial prophylaxis but is effective in reducing inflammation. The low blood levels of doxycycline are unlikely to result in the emergence of antibiotic resistance.

Contraindications: Apprilon is contraindicated in:

- Patients hypersensitive to any component of Apprilon
- The 2nd or 3rd trimester of pregnancy and in lactation
- Children < 8 years of age
- Patients with myasthenia gravis

Warnings & Precautions: Apprilon should:

- Not be used for the treatment or prophylaxis of bacterial infections
- Not be used for patients with achlorhydria, gastrectomy patients, patients with gastric bypass, and patients who have undergone duodenal bypass or removal
- Be administered cautiously to patients with hepatic impairment or in combination with potentially hepatotoxic products
- Not be given to patients predisposed to candidiasis
- Be stopped in patients experiencing watery or bloody diarrhea or fever or abdominal pain/tenderness

Patients should minimize or avoid sun exposure or use of tanning beds when taking Apprilon due to possible phototoxicity. Use of a sunscreen is recommended.

Drug Interactions: No drug interaction studies were conducted with Apprilon, but the product monograph lists the same drug interactions as other doxycyclines, as follows:

- Impaired doxycycline absorption may occur with concomitant administration of bismuth subsalicylate, proton pump inhibitors, quinapril (due to high magnesium content), antacids (containing aluminum, calcium, or magnesium), iron preparations, enzyme inducers (e.g., rifampicin, barbiturates, carbamazepine, phenytoin, chronic alcohol abuse, etc.), and cyclosporine.
- Oral retinoids combined with doxycycline may increase the risk of pseudotumor cerebri and should be avoided.
- Doxycycline is bacteriostatic and may interfere with the bactericidal action of β-lactam antibiotics including penicillin.
- Doxycycline may increase the INR in warfarin patients.
- A second form of contraception is advised in patients taking oral contraceptives and Apprilon.
- Doxycycline may potentiate the hypoglycemic effects of oral sulfonylureas. Monitoring is advised.

Adverse Effects: Most commonly reported adverse effects include diarrhea (4%), abdominal pain (2%), fungal infection (2%), increased aspartate aminotransferase (AST; 1.5%) and upset stomach (1%).

Dose & Administration: The recommended adult dose is 40 mg (1 capsule) once daily in the morning with a full glass of water. Higher doses are not more effective. Apprilon should be taken on an empty stomach, preferably at least 1 hour before or 2 hours after a meal. Taking the dose with an inadequate amount of fluid may result in esophageal irritation and/or ulceration. Dairy products and calcium-containing fruit juices may impair the absorption of doxycycline and thus should be taken 2 to 3 hours after Apprilon. Concomitant absorption with food significantly reduces absorption.

Availability & Storage: Apprilon is available in boxes containing 28 blister packed capsules and should be stored from 15 to 30°C in the original package to protect from light. DN

(Refer to the product monographs for complete information.)