Drug Monitor

Maximizing Clopidogrel's Benefits

For a patient with ST-elevation myocardial infarction (STEMI) who undergoes primary percutaneous coronary intervention (PPCI), clopidogrel is likely to provide the greatest benefit if it is delivered before PPCI and at a dose of 600 mg.

That was the conclusion of researchers from Sunnybrook Health Sciences Centre, Toronto, Canada; Sheba Medical Center, Tel Hashomer, Israel; Rambam Medical Center, Haifa, Israel; and Tel Aviv University Sackler School of Medicine, Tel Aviv, Israel after studying 383 patients with STEMI. Of these patients, 57% received clopidogrel loading before undergoing PPCI and 43% received it after PPCI. The patients' clopidogrel dosage was either 600 mg (received by 54% of patients in the before-PPCI group and 56% of those in the after-PPCI group) or 300 mg (received by 46% of patients in the before-PPCI group and 44% of those in the after-PPCI group). The researchers set out to determine whether the endpoint of recurrent acute coronary syndrome, stent thrombosis, congestive heart failure, or death at one month was associated with either the timing or the dosage of clopidogrel loading.

They found that a decreased incidence of the endpoint was associated with both before-PPCI loading and the 600-mg dosage. The endpoint occurred in 22% of patients who received clopidogrel loading before PPCI, compared with 34% of those who received it after PPCI ($P = .008$). This association persisted after adjustment for baseline characteristic differences, previous coronary disease, Killip class, extent of coronary artery disease, use of glycoprotein IIb/IIa antagonists, ischemic time, and propensity score. The endpoint occurred in 21% of patients who received a 600-mg dosage, compared with 31% of those who received a 300-mg dosage ($P < .01$).

In addition, the researchers found a "graded outcome" when they stratified the patients into four groups based on both the timing and the dosage of clopidogrel loading. The endpoint occurred in 16% of patients who received 600 mg before PPCI, 27% of patients who received 300 mg before PPCI, 28% of patients who received 600 mg after PPCI, and 39% of patients who received 300 mg after PPCI.

The researchers conclude that clopidogrel timing and dosage have an important impact on outcomes. They add that this finding "might have an even greater effect as newer generations of more potent thienopyridines with more rapid onset of action become available."

Source: *Am J Cardiol.* 2009;104(4):514–518. doi:10.1016/j.amjcard.2009.04.013.

Tamsulosin Use in the ED

Studies have shown that alpha-blocking agents such as tamsulosin can improve the passage of ureteral stones—and that adverse effects from these agents are infrequent. So how often do emergency department (ED) physicians treat ureteral stones with tamsulosin, and what factors influence whether or not they do so?

To find out, researchers from Advocate Christ Medical Center, Oak Lawn, IL distributed electronic or paper surveys to 240 ED physicians in five states. The physicians were asked about their use of tamsulosin treatment for ureteral stones, their length of time in practice, and the type of hospital where they worked. They also were asked to write in factors that influenced their use or nonuse of the treatment.

Of the 103 physicians who responded to the surveys (43%), 60% said they used tamsulosin in fewer than 25% of patients with ureteral stones. In addition, 27% of respondents said they had not heard that tamsulosin could be used to treat ureteral stones. Other factors associated with infrequent use of the treatment included being unsure of its formal urology recommendations, questioning its supporting data, forgetting to administer it, and being unsure of its contraindications. Although practice in a county hospital was associated with infrequent use of the treatment, the physicians' length of time in practice was not.

Overall, the researchers conclude, the use of tamsulosin therapy appears inconsistent, "suggesting that significant barriers to new therapeutic options may exist."

Source: *Am J Emerg Med.* 2009; 27(7):776–778. doi:10.1016/j.ajem.2008.06.007.

Actovegin for Diabetic Neuropathy

Diabetic distal symmetric polyneuropathy (DPN) is associated with excruciating pain and can decrease quality of life substantially, say researchers from University Hospital, Düsseldorf, Germany; Nycomed, Roskilde, Denmark; Ministry of Public Health of Ukraine, Kiev, Ukraine; Federal Bureau of Medical and Social Expertise and Sechenov Moscow Medical Academy, both in Moscow, Russia; and Scientific Research Institute of

Cardiology, Almaty, Kazakhstan. But after performing a randomized, double-blind clinical trial at 26 medical centers in three countries, they found that actovegin, a deproteinized hemoderivative, can help to mitigate DPN symptoms.

Their trial included 567 patients with type 2 diabetes and DPN. Of these patients, 281 were assigned to receive actovegin and 286 were assigned to receive placebo. The actovegin regimen consisted of 20 intravenous infusions (actovegin 20% with 8 mg/mL in a 250-mL sodium chloride 0.9% solution; at an infusion rate of 2 mL/min) administered once daily over the course of 20 to 36 days, followed by oral actovegin 600 mg (in three 200-mg tablets) three times daily for 140 days. The control regimen was identical, with placebo intravenous solution and tablets used.

The two primary endpoints of total symptom score (TSS) and vibration perception threshold (VPT) were measured at screening, every fifth infusion visit during intravenous treatment, and every four weeks during oral treatment. Secondary outcomes included neuropathy impairment score of the lower limbs (NIS-LL), which was measured at the same time as the primary endpoints, and quality of life, which was assessed using the short form-36 questionnaire at randomization and after the intravenous and oral treatment periods. Patients were asked about adverse events at every visit.

The researchers found that actovegin resulted in significant improvements compared to placebo. As averaged over the course of the trial, TSS was 0.56 points lower and VPT was 3% lower in the actovegin group than in the placebo group. When reductions in these scores between baseline and 160 days were compared, TSS reductions were 0.86 points lower and VPT reductions were 5% lower in the actovegin group than in the placebo group. NIS-LL sensory function and the SF-36 mental health domain also showed significant improvements in the actovegin group compared with the placebo group. The incidence of adverse effects did not differ between the groups.

The researchers note that the mechanisms of actovegin's benefits to nerve function have yet to be established. Nevertheless, they say, "there is direct and indirect evidence to support the notion that actovegin exerts an insulin-like effect leading to enhancement of glucose utilization."

Source: *Diabetes Care*. 2009;32(8):1479–1484. doi:10.2337/dc09-0545.

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