Drug Monitor

Another Tool for Fighting *Staphylococcus aureus* Bacteremia

The growing problem of bacteremia and endocarditis caused by methicillin resistant *Staphylococcus aureus* (MRSA) infection is compounded by reports of bacterial resistance and suboptimal response to standard vancomycin treatment, say researchers for the *S. aureus* Endocarditis and Bacteremia Study Group. To find out whether the cyclic lipopeptide antibiotic daptomycin might be a viable alternative, the researchers pitted this drug against the standard therapy in an international, multisite, open-label, randomized trial.

Of the 235 adults with positive *S. aureus* blood cultures included in the modified intent-to-treat analysis, 120 were given daptomycin 6 mg/kg IV once daily. The other 115 received standard therapy, which consisted of either vancomycin 1 g every 12 hours (with appropriate dose adjustment) or an antistaphylococcal penicillin (nafcillin, oxacillin, or flucloxacillin) 2 g every four hours, depending on the infecting organism's methicillin susceptibility. In addition, the study protocol called for all patients in the standard therapy group and those in the daptomycin group who had left-sided endocarditis to be given gentomycin 1 mg/kg IV every eight hours (or adjusted according to renal function) for the first four days.

By 42 days after the end of treatment, 53 (44.2%) of the daptomycin patients and 48 (41.7%) of the standard therapy patients had achieved a successful clinical outcome—thus establishing the noninferiority of daptomycin therapy. Although the differences were nonsignificant, success rates in patients with MRSA infections were slightly better with daptomycin therapy, whereas those in patients with methicillin susceptible *S. aureus* (MSSA) infections were slightly better with standard therapy.

S. aureus infection either persisted or recurred in 16% of patients taking daptomycin, compared with 10% of those taking standard therapy. The researchers point out, however, that many of the treatment failures were attributed to factors other than lack of efficacy. For example, not having had a blood culture drawn at the day 42 visit, even in the absence of clinical evidence of persistent or relapsing *S. aureus* infection, contributed to the high failure rates in both groups.

Based on the results of this trial, the FDA has approved daptomycin for the additional indication of treating *S. aureus* bloodstream infections, including right-sided endocarditis caused by MSSA or MRSA, at the dosage of 6 mg/kg IV once daily. (The drug was first approved in 2003, at a dosage of 4 mg/kg once daily, for treating complicated skin and skin structure infections caused by Gram-positive organisms.) Because of a significantly higher incidence of creatine kinase elevations associated with daptomycin treatment, the researchers advise monitoring patients taking daptomycin for such elevations and for skeletal muscle dysfunction.

Sources: *N Engl J Med.* 2006;355:653–665.

Cubist Pharmaceuticals news release. May 25, 2006.

Morphine and Ketorolac: Better Together?

In patients with renal colic, a combination of morphine and ketorolac work better than either drug alone, according to researchers from Yale University School of Medicine and Hospital of Saint Raphael, both in New Haven, CT, and the Mount Sinai School of Medicine in New York, NY. Their randomized, double-blind study was the first to compare IV ketorolac with IV morphine in the setting of renal colic.

Of the 130 patients who met the eligibility criteria of age between 18 and 55 years, clinical diagnosis of acute renal colic, and patient pain rating of 5 or more on a 10-cm visual analogue scale or at least "moderate" on a four-category verbal pain scale, 43 were assigned to receive morphine 5 mg IV, 43 were assigned to receive ketorolac 15 mg IV, and 44 were assigned to receive both drugs. Patients' pain was reassessed at 20 minutes after the initial dose, and those with continuing pain received a second dose of their assigned medication. The primary outcome measurements were reduced pain and the need for rescue analgesia (an extra 5 mg of IV morphine) at 40 minutes.

After 20 minutes, 30% of the patients in the combination therapy group had their pain relieved without a second dose of medication. By contrast, 16% of the morphine patients and 11% of the ketorolac patients were pain free after the first dose. At 40 minutes, the mean pain scores on the visual analogue scale were 3.7 cm for the morphine group, 4.1 cm for the ketorolac group, and 2 cm for the combination group. Rescue morphine was required by 42% of the morphine patients, 33% of the ketorolac patients, and 16% of the combination therapy patients.

Patients receiving morphine alone were more likely than those receiving either of the other two treatments to have an adverse event. The most

Continued on page 35

Continued from page 31

common adverse events were nausea, dizziness, and vomiting. The researchers found no significant differences between the groups with regard to changes in blood pressure, pulse rate, respiratory rate, or oxygen saturation.

The researchers say that their results support a synergism between nonsteroidal anti-inflammatory drugs and opioids that has been demonstrated previously in animal studies and postoperative settings. Based on their findings, they note that either morphine 5 mg IV or ketorolac 15 mg IV probably is inadequate as an initial treatment of acute renal colic. They suggest future research comparing combination therapy with morphine 0.1 mg/kg IV and ketorolac 30 mg IV.

Source: *Ann Emerg Med.* 2006;48:173–181.

Effects of HIV Drugs on Serum Urate Levels

Studies have found that HIV-infected patients are prone to imbalances in serum uric acid. Low levels have been attributed to increased renotubular loss, whereas high levels may be due to increased cell turnover. But antiretroviral drugs also should be considered as possible contributors, say researchers from Medizinische Universitätsklinik, Freiburg; Ifi Institute, Hamburg; and Hannover Medical School, Hannover; all in Germany. Noting that didanosine is known to cause hyperuricemia, they examined the effects of other antiretroviral drugs as well.

The researchers prospectively measured urate levels in 270 patients with HIV infection over the course of 2,287 visits and performed statistical analyses to uncover possible associations with a number of variables. In addition to verifying the influence of gender, renal function, and body mass index on urate levels, their findings also revealed a "quantitatively important" impact of some antiretroviral agents.

Didanosine, stavudine, and zalcitabine were associated with an increase in urate levels. Stavudine had the strongest effect, and patients treated with a combination of stavudine and didanosine had significantly higher levels compared with patients taking didanosine or stavudine along with another nucleoside reverse transcriptase inhibitor. Tenofovir disproxil fumarate taken without didanosine was associated with lower urate levels. The urate levels of patients taking tenofovir plus didanosine were lower than those taking didanosine without tenofovir and similar to those of control patients not taking antiretroviral drugs.

The researchers also found a small but independent link between protease inhibitors and serum urate level elevation. Boosted protease inhibitors have been associated previously with a higher incidence of gout, they note—adding that, in people without HIV, gout is associated with the presence of hyperlipidemia, insulin resistance, and central adiposity, all symptoms characteristic of protease inhibitor therapy. Given that people infected with HIV may have a higher incidence of gout, the researchers conclude that the impact of antiretroviral drugs on serum urate levels may be of clinical relevance.

Source: *AIDS.* 2006;20:1556–1558 [research letter].

Early Data on Argatroban

Preliminary results are in on argatroban, a direct thrombin inhibitor that augments the benefits of recombinant tissue plasminogen activator (rtPA) in acute stroke. According to the ongoing Argatroban tPA Stroke Study, low dose argatroban, combined with IV rtPA, appears to be safe and may produce faster, better recanalization than rtPA alone.

In this study, 10 (71%) of the 14 patients given both drugs had achieved any recanalization by two hours, and six (43%) had achieved complete recanalization by this time. By 48 hours, all patients had achieved some degree of recanalization and 12 (86%) had achieved complete recanalization. Reocclusion occurred in three patients (21%)—but one of these had subsequent recanalization.

Although not statistically significant, these results show a trend toward improved recanalization with rtPA plus argatroban when compared with an rtPA-alone control group from the researchers' earlier Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic tPA (CLOTBUST) trial. In this study, 38% of the patients achieved any recanalization and 17% achieved complete recanalization by two hours.

Rates of parenchymal hemorrhage were similar between the present study patients (6%) and the CLOTBUST study controls (5%). Symptomatic intracerebral hemorrhage was more common in the present study (13% versus 5% among CLOTBUST study controls).

One of argatroban's advantages compared with other thrombin inhibitors, the researchers say, is its short half-life, which allows for rapid offset of action in case of bleeding and easier monitoring of its antithrombotic effect by means of the activated partial thromboplastin time.

These are the first trials of artgatroban in humans. The patient sample was small, however, and the researchers acknowledge the need for larger trials. The second phase of the study will enroll 50 more patients. ●

Source: *Arch Neurol.* 2006;63:1057–1062.