Dosing Antimicrobials for Heavier Patients

Does a patient's weight affect the efficacy of an antimicrobial drug? It's hard to tell but important to know, say researchers from Pfizer Inc. in Collegeville, Pennsylvania; Creighton University Medical Center in Omaha, Nebraska; and Rochester Methodist Hospital in Minnesota. For instance, a patient's weight can affect hydrophilic drugs like vancomycin, because adipose tissue is composed of about 30% water. Moreover, getting the dose right may be even more important in patients who are overweight, because they may be at a higher risk for nosocomial infections, compromised healing, and impaired circulation.

The researchers point out that clinical studies often exclude patients who are overweight or obese, limiting the available amount of pharmacokinetic and pharmacodynamic information. And that makes choosing the best dose for patients with serious infections much harder.

To find out if weight matters—and if so, how much—the researchers analyzed findings from 2 clinical trials of 1,079 patients with complicated skin and skin structure infections (cSSSIs) or nosocomial pneumonia (NP). The patients, who were randomized to receive a fixed dose of linezolid or weight-based vancomycin (15 mg/kg intravenously [IV] every 12 hours), were stratified into quartiles according to weight (Q4 was the highest: 97-295 kg for the cSSSI cohort and 88-215 kg for the NP cohort). Seven to 30 days after the end of treatment, clinical response was assessed by weight and by type of treatment. Microbiologic response was assessed at the end of treatment and at the end of the study.

Overall, linezolid was safe and effective at 600 mg every 12 hours, for both cSSSIs and NP caused by methicillin-resistant *Staphylococcus aureus* (MRSA), regardless of the patient's weight. The rates of clinical and microbiologic success were similar for vancomycin-treated patients across the weight quartiles. However, the study data also indicated that clinical success rates for vancomycin-treated patients with cSSSIs were significantly lower compared with linezolid in the highest weight quartile (70% vs 86%, $P = .03$) but remained similar among patients with NP. Those findings are significant, the researchers say, because of a lack of clinical efficacy data related to both a fixed-dose and weight-based dose treatment for MRSA infections.

The mean vancomycin trough concentrations at day 3 were higher in the heaviest patients compared with the lower quartiles, and the trough concentrations were higher at day 7 compared with day 3 for all quartiles. Other than the second quartile at day 3, the vancomycin concentrations were within the therapeutic range recommended by the Infectious Diseases Society of America. Those data suggest that the weight-associated decline in efficacy with vancomycin was not related to a decrease in drug concentrations, the researchers say.

Among the patients with NP, the highest vancomycin trough was in the higher weight quartiles and reached the higher threshold at day 6, but the outcome in the top quartile compared with the bottom quartile did not differ significantly. That suggests, according to the researchers, that the weight-based algorithm may have a threshold of effectiveness related to weight—that is, lower weights may be underdosed or actual weight may not be the most effective dosing parameter.

The Q1 patients (weight, 40-63 kg) with NP had the lowest rate of clinical success with vancomycin. Lower weight may be a proxy for other factors, such as older age and overall debilitation; evidence is mounting that low weight may be a risk factor for acquiring infections and having poorer outcomes, the researchers note.

Adverse events (AEs) were consistent with the known safety profiles of each drug regardless of weight quartile. Numerically, more patients in Q1 and Q2 (92% each) experienced AEs compared with Q3 (88%) and Q4 (86%). In Q2 through Q4, more patients in the linezolid group experienced AEs. Two patients in Q2 (1 in each treatment group) had anemia; 16 patients had thrombocytopenia (10 receiving linezolid and 6 receiving vancomycin). Incidence of renal impairment was similar between the 2 indications, although lower in all quartiles of linezolid-treated patients.

The researchers note that limitations to their analysis included the lack of data on patient height. As a result, they were not able to calculate body mass index (BMI), compare percent body mass, or distinguish fat mass from lean mass. On the other hand, they add, there is limited guidance about a standardized dosing regimen and which parameter to consider when dosing in patients with varying weights (eg, lean body weight, total body weight, and BMI). The weight analysis also did not take into account sex differences. Despite such limitations, however, the researchers conclude that their analysis provides additional clinical evidence about the impact of weight on treatment outcomes. ●

Source: Puzniak LA, Morrow LE, Huang DB, Barreto JN. *Clin Ther.* 2013;35(10):1557-1570. doi: 10.1016/j.clinthera.2013.08.001.