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EDITORIAL

Limited Monitoring of Vancomycin Concentrations in Pediatric Patients

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In this issue of the journal, Lee and Phelps[1] describe the results of a study in which all requests to monitor vancomycin concentrations in a pediatric hospital were referred to the Pharmacokinetic Service which approved or denied the request based on pre-determined criteria. Trough concentrations were approved for infants under the age of 3 months, those receiving more than 60 mg/kg/day, and in children who were critically ill, had renal dysfunction or were receiving concurrent nephrotoxic drugs. Peak and trough concentrations were acceptable in burn patients or those who failed to respond clinically within 72 hours. The investigators compared the number of vancomycin concentrations as well as measures of clinical outcome in the 2-month period prior to and following the implementation of monitoring criteria. The percentage of patients who had vancomycin concentrations monitored decreased from 65% to 32% after implementing the criteria, while the number of concentrations decreased from 113 to 39. The reduction in vancomycin concentrations was not associated with any statistically significant changes in measures of patient outcome including white blood cell count, serum creatinine, or BUN.

Reports questioning the value of routine vancomycin concentration monitoring in adults first appeared in the literature in 1987[2] with an increasing number of authors questioning this practice throughout the early 1990s. The issues concerning vancomycin monitoring in uncomplicated patients with stable renal function revolve around the following questions:

1. Is the disposition of the drug so variable that plasma concentrations with standard doses cannot be predicted?
2. Is there a narrow range between concentrations required for efficacy and those associated with toxicity?

Unless the answer to both of these questions is yes, there is little justification for measuring plasma concentrations. Although vancomycin clearance varies between patients, much of this variability is related to renal function and can be accounted for by basing doses on estimated creatinine clearance. With respect to the reference range, research over the past decade has indicated that vancomycin kills bacteria in a time-dependent manner, and the most effective dosing strategies are those that maintain concentrations above the minimum inhibitory concentration (MIC) throughout the dosing interval. Given that MICs are typically less than 2 mg/L, maintaining trough concentrations in the range of 5-15 mg/L should be effective in most patients. Unfortunately, there has been little new data linking toxicity to specific plasma concentrations. Although there is a relationship between the magnitude of drug exposure and toxicity, both nephrotoxicity and ototoxicity are uncommon when dosing is individualized to achieve therapeutic trough concentrations. Such individualization can be achieved using nomograms that take into account the renal function and body size of the patient. Using decision-analysis to model the cost-effectiveness of vancomycin monitoring, Darko et al.[3] suggested this practice could only be justified in patients in

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the intensive care unit or those receiving concomitant nephrotoxic drugs.

Pediatric practitioners have been slower to embrace the concept of limited vancomycin monitoring. This may be due to concerns that more rapid clearance and a faster half-life of vancomycin in children could lead to sub-therapeutic concentrations with standard dosing regimens. The solution to this problem, however, is not more intensive monitoring but rather the development and use of appropriate dosing nomograms that take these factors into account. There may also be concerns that the disposition of vancomycin in children is more unpredictable than in adults. Even if this were true (and there appears to be little evidence to this effect), the reference range of vancomycin does not appear to be particularly narrow. It should not be difficult to design a regimen that will produce, in most uncomplicated patients, a trough concentration between 5 and 15 mg/L. Unless the volume of distribution is strikingly abnormal, very few patients with a therapeutic trough concentration will have a peak concentration above values that have been associated with toxicity.

The paper by Lee and Phelps demonstrated that vancomycin monitoring in their institution was excessive when evaluated using criteria for monitoring that are supported by the literature. By implementing a review process prior to collection of samples, the number of unnecessary concentrations was substantially reduced with the potential for considerable cost-savings. In addition, the investigators took the additional step of assessing whether or not reduced monitoring compromised patient care. While the fact that there was no discernible change in patient outcome is somewhat reassuring, it should be noted that demonstrating a link between therapeutic drug monitoring and patient outcome is a challenge. There are many factors other than plasma concentration that influence response to an antibiotic, and this particular study was not designed to evaluate the appropriateness of vancomycin dosing or plasma concentrations. In fact, a higher percentage of patients had therapeutic trough concentrations of vancomycin in the 2-month period prior to the implementation of monitoring criteria. In addition, not all patients had positive cultures for organisms sensitive to vancomycin, and close to 40% of the patients received vancomycin for less than 72 hours. Given these limitations, one must be cautious in interpreting the conclusions regarding the impact of reduced monitoring on patient outcome. However, since more intensive monitoring in uncomplicated patients has not been shown to improve patient care, the criteria outlined in Table 1[1] would seem to be a reasonable and cost-effective approach to monitoring vancomycin plasma concentrations in children.

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