JFP Journal Club

VANCOMYCIN DOSING

TITLE: The appropriateness of initial vancomycin dosing
AUTHORS: Rodman DP, McKnight JT, Rogers T, Robbins M
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Background: Vancomycin use is growing, primarily because of the increasing prevalence of methicillin-resistant staphylococcal infections. The drug has a relatively narrow therapeutic range (recommended peak level of 20 to 50 mg/dL, recommended trough of 5 to 15 mg/dL). Elevated levels are associated with ototoxicity and nephrotoxicity, primarily when the patient is also receiving a second nephrotoxic drug such as an aminoglycoside.[1] However, there is little objective evidence that vancomycin alone causes significant ototoxicity or nephrotoxicity, or that elevated drug levels are closely related to toxicity.[2] Although the drug level depends on a patient's weight and renal function, these factors are often not considered by physicians when choosing a dosage and dosing interval. While dosing nomograms have been developed to assist physicians in this process, they are not widely used.[3]

Clinical questions: 1. How accurately do physicians dose vancomycin in adult patients? 2. Does use of a dosing nomogram have the potential to increase the number of patients with therapeutic drug levels?

Population studied: Consecutive adult patients (over a 3-month period) in a community-based teaching hospital who received vancomycin and had at least one subsequent serum level.

Study design and validity: For each patient meeting the entry criteria, age, weight, height, sex, serum creatinine, blood urea nitrogen, physician type (resident or attending), and initial vancomycin dosage were recorded. The creatinine clearance was estimated using the following equation:

$$\text{Creatinine clearance} = \frac{(140 - \text{age}) \times (\text{ideal body weight})}{\text{serum creatinine} \times 72} \; (\times 0.85 \text{ if female})$$

This value was then used in the nomogram to identify the most appropriate initial vancomycin dosage and dosing interval (Table).

The recommended initial dosage and dosing interval were compared with those actually ordered. If a patient had a nontherapeutic peak or trough, the elimination half-life and apparent distribution volume were calculated from serial serum vancomycin levels. This information was used to *estimate* the peak and trough that would have been obtained using the initial dosage and dosing interval recommended by the nomogram.

Outcomes measured: There were two primary outcome measures: the number of patients with therapeutic peak and trough levels of vancomycin following the initial dose, and an estimate of the number of patients who would have had a therapeutic peak and trough if the dosing nomogram had been used.

Results: Of 48 patients who met the entry criteria, only 19 had therapeutic peak and trough levels. Of the remainder, 16 had a trough that was too high or too low, and 18 had a peak that was too low. Older patients were more likely to have a trough level above 15 (potentially toxic), while younger patients were more likely to have an inadequate trough level (potentially nontherapeutic). It was estimated that 22 of the 29 patients with inaccurate dosing would have achieved therapeutic peak and trough levels had the nomogram been used.

Recommendations for clinical practice: This study provides preliminary evidence that use of the nomogram may improve the accuracy of vancomycin dosing in adult patients. However, the evidence would be more convincing if the patients had been randomized to either the nomogram or standard dosing, and patient-oriented outcomes, such as the length of stay, morbidity, or mortality, had been measured. Since dosing by nomogram requires no more effort than traditional dosing and does

Table. Estimated Appropriate Vancomycin Dosages and Dosing Intervals (Initial dosage: 15 to 19 mg/kg [based on total body weight])

Creatinine Clearance (mL/min)	Dosing Interval (hours)
>94	12
75–94	18
55–74	24
35–54	36
25–34	48
<25	*

**Single dose; then adjust based on serum concentrations.*

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not appear to expose patients to additional risk or cost, use of the nomogram can be recommended in older patients, those with impaired renal function, and those also receiving an aminoglycoside. This study does not provide justification for monitoring vancomycin levels once a dosage and interval are chosen, since that issue was not addressed.

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HEPARIN THERAPY

TITLE: The weight-based heparin dosing nomogram compared with a "standard care" nomogram: a randomized controlled trial
AUTHORS: Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S
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Background: Heparin therapy is the mainstay of treatment for thromboembolic disease. Several studies have provided evidence that achieving a therapeutic level of anticoagulation more rapidly results in a lower rate of recurrent thromboembolism for up to 3 months, giving added importance to accurate dosing in the early phases of hospitalization.[1,2] This late benefit of rapid anticoagulation may be related to protection by fibrin of clot-bound thrombin from inactivation by heparin-antithrombin III complexes.[3]

Clinical question: Does dosing heparin based on weight rather than standard care result in more rapid achievement of anticoagulation and a reduced rate of recurrence of thromboembolism?

Population studied: The study was set in two community teaching hospitals in Rochester, New York, and Phoenix, Arizona. Inclusion criteria: adult patient with pulmonary embolism (PE) diagnosed by a high-probability ventilation-perfusion (VQ) scan or arteriography, a proximal deep vein thrombosis (DVT), unstable angina, or other acute noncoronary arterial ischemia. Exclusion criteria: anticoagulant within the past 7 days or other risk for bleeding. Thus, patients with an intermediate probability VQ scan were excluded, a group sometimes anticoagulated but with a lower probability of disease. Overall, the population in this study was representative of that cared for by primary care physicians and was not overly selected.

Study design and validity: The study was a randomized controlled trial. Patients were randomized to standard care or the weight-based dosing schedule, and the activated partial thromboplastin time (APTT) was checked every 6 hours. The nurses who weighed the patients, calculated doses, and adjusted the infusion rate were not blinded to the protocol, introducing a possible bias. For example, if they "preferred" a particular protocol, they could either initiate heparin dosing more quickly or check APTT levels more frequently in those patients. The two protocols are shown in the Table.

Outcomes measured: The time required to achieve a therapeutic level of anticoagulation (1.5 to 2.3 times control), the number of patients achieving a therapeutic level by the first blood draw and at 24 hours, and the rate of in-hospital complications were measured. Patients with a discharge diagnosis of venous thromboembolism were followed for 3 months by blinded researchers to identify the number of venous thromboembolic recurrences, defined as confirmed episodes of deep venous thrombosis or pulmonary embolism.

Results: Of the 121 eligible patients, 115 agreed to participate and 100 received at least 48 hours of heparin. The majority (85 of 115) had either PE or DVT. The two groups were not treated differently by the nurses

Table. Two Protocols for Heparin Dosing

APTT Results	Standard Care	Weight-Based Dosing
Initial	5000 unit bolus, then 1000 U/h	80 U/kg bolus, then 18 U/kg/h
APTT <35 sec	5000 unit bolus, then 200 U/h	80 U/kg bolus, then increase rate by 4 U/kg/h
APTT 35–45 sec	2500 unit bolus, then 100 U/h	40 U/kg bolus, then increase rate by 2 U/kg/h
APTT 46–70 sec	No change	No change
APTT 71 to 90 sec	Decrease rate by 100 U/h	Decrease rate by 2 U/kg/h
APTT >90 sec	Hold infusion 1 hour, then decrease rate by 200 U/h	Hold infusion 1 hour then decrease rate by 3 U/kg/h

based on the number of APTT measurements, timing of the doses, and number of dosing errors, and they had a similar rate of complications. By every measure, the patients in the group using the weight-based nomogram achieved a therapeutic level of anticoagulation more rapidly than those in the standard care group: mean time to exceed the threshold of 1.5 times the APTT (8.2 hours vs 20.2 hours, $P < .001$); percentage exceeding the threshold on the first APTT draw (86% vs 32%, $P < .001$); mean duration before achieving a value in the therapeutic range (14.1 hours vs 22.3 hours); and percentage achieving a value in the therapeutic range at 24 hours (89% vs 75%, $P = .08$). Most important, patients in the group receiving standard care had a higher recurrence rate of thromboembolism during the 3-month follow-up period than those treated using the weight-based nomogram (relative risk 5.0, 95% confidence interval [CI] 1.1 to 21.9, $P = .02$).

Recommendations for clinical practice: Other than a minor concern regarding blinding, the study methodology is valid and the outcomes measured are patient-oriented. Therefore, heparin dosing using a simple weight-based nomogram can be recommended to primary care physicians, since it has been shown to significantly reduce the rate of recurrence of thromboembolic disease in a population of patients typical of those seen by family physicians.

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