No influence of large volume blood loss on serum vancomycin concentrations during orthopedic procedures

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We prospectively studied orthopedic patients with either large or small blood loss who also received vancomycin prophylaxis to determine the effect of intraoperative volume shifts on serum vancomycin concentrations. There were 6 index patients in the large blood loss group (greater than 2 L), and 7 in the control group (less than 2 L). Mean estimated blood loss for index and controls was 4.4 L and 1.0 L, respectively. Mean intraoperative fluid resuscitation, excluding blood products, was 12.4 L and 5.1 L, respectively.

There was a modest inverse correlation between blood loss and intraoperative serum half-life of vancomycin. Although controls maintained slightly higher intraoperative vancomycin concentrations at each time-point, there was no statistically significant difference between the groups with regard to absolute concentrations or rate of decline. After 8 hours, the serum vancomycin concentration exceeded the MIC-90 for *Staphylococcus aureus* by approximately eightfold in all but one case patient. This was a morbidly obese patient with massive blood loss. Thus, blood loss during orthopedic procedures has minimal effects on intraoperative kinetics of vancomycin. Redosing is rarely indicated, although a preoperative 1.5 gram-dose should be considered for patients weighing more than 90 kg.

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For prophylactic antibiotics to be most effective, adequate serum and tissue concentrations should be maintained throughout the operative procedure (Fitzgerald and Washington 1975, Mader and Cierny 1984). The particular antibiotic regimen is dictated by factors which include drug half-life, toxicity profile, and activity against likely pathogens. The organisms most often implicated in orthopedic postoperative wound infections are *Staphylococcus aureus* and coagulase-negative staphylococci. The prevalence of methicillin-resistant staphylococci in many hospitals has dictated that prophylactic vancomycin be used for certain high-risk individuals (Johnson and Johnston 1986, James et al. 1994).

Large volume blood loss during orthopedic procedures may increase the clearance of antibiotics distributed in the extracellular space. In addition, administration of large volumes of intravenous fluids may further dilute the concentration of antibiotics in the body. A concern is that these combined effects will reduce serum antibiotic concentrations, compromising antimicrobial prophylactic efficacy late during prolonged operative procedures. To minimize this anticipated dilutional effect, surgeons occasionally shorten the dosing interval during prolonged procedures. We determined whether large intraoperative volume shifts among patients undergoing orthopedic procedures cause serum vancomycin concentrations to fall below therapeutic levels.

Patients and methods

13 evaluable patients were studied, including 7 index and 6 controls. Index and controls did not differ at baseline with regard to age, weight, serum albumin, creatinine, or creatinine clearance. This study was approved by the medical center Institutional Review Board. Consecutive patients over a 2-month period were considered for enrollment if they were to have an orthopedic procedure with large anticipated blood loss (> 2 L) or a prolonged procedure (> 6 hours) with minimal blood loss. Patients enrolled were between 18 and 65 years of age and gave informed consent (Table 1). Routine preoperative assays included serum electrolytes, albumin, creatinine, total protein,

complete blood cell count, and urinalysis. Patients with renal insufficiency, defined as estimated creatinine clearance less than 60 mL/min, using the Cockcroft-Gault equation (Cockroft and Gault 1976), or a history of vancomycin allergy, were excluded.

The large blood-loss group (index) was defined as patients undergoing orthopedic procedures with estimated blood loss greater than 2 L. A control group included patients scheduled to undergo prolonged procedures, with expected blood loss less than 2 L.

1 hour prior to surgical incision, 1 g of vancomycin was administered intravenously over 30 minutes. Any side-effects were documented. Blood was obtained from an arterial line hourly throughout the procedure, beginning 1 hour after the infusion. Whole blood samples were collected into red-top tubes and placed on ice until centrifuged. Serum was stored at 4 °C until assayed within 48 hours. Redosing of antibiotics during the procedure, if deemed necessary, utilized a drug other than vancomycin, so as not to interfere with the assays. Volumes of blood and urine lost intraoperatively, and volumes of intravenous fluids, packed red blood cells, and other blood replacement products administered were documented by an anesthesiologist.

Serum vancomycin concentrations were quantitated by ELISA, using an automated methodology (Abbott TDX, Abbott Laboratories).

Estimated creatinine clearance was calculated using the formula of Cockcroft and Gault (1976). The elimination half-life of vancomycin was determined for each subject by plotting serum vancomycin concentration versus time on a semilog scale and applying a best-fit line through the log linear range. Concentrations over time were compared by calculating the average area under the curve (AAUC) for each patient.

Statistics

Continuous variables were compared with the Student's t-test, with the Wilcoxon sign rank test, or with Spearman's correlation coefficient, as appropriate (SPSS Statistical Software Program, Chicago, IL). All statistical tests were two-tailed.

Table 1. Results (mean and 95% CI) in high (n 7) and low blood-loss cases (n 6)

	High blood loss	Low blood loss	P-value
Age, years	48 (42–54)	53 (46–60)	NS
Creatinine (mg/dL)	0.86 (0.60–1.11)	0.72 (0.59–0.84)	NS
Weight, kg	80 (63–97)	73 (52–94)	NS
Creatinine clearance, mL/min	98 (74–122)	88 (63–114)	NS
Albumin, g/dL	3.5 (2.2–4.8)	4.2 (2.9–5.5)	NS
Procedure duration, hours	8.4 (6.4–10.5)	8.4 (6.1–10.7)	NS
IV fluids, L	12.5 (7.5–17.4)	6.9 (3.0–10.8)	0.05
Blood administered, units	6.4 (0.7–12.2)	1.3 (0–3.5)	0.04
Blood loss, L	4.4 (1.3–7.6)	0.97 (0.36–1.6)	0.001
Urine output, L	1.7 (1.1–2.3)	2.3 (0.45–4.1)	NS

Table 2. Summary of operative procedures and intraoperative volume shifts

Procedure	Duration hours	Fluids L	Blood given units	Blood loss L	Urine L
Cases					
Scoliosis	10	12	2	2	1.7
Revision THA	6	8.5	3	2.1	2.2
ORIF pelvis	7	6.5	4	2.3	0.8
ORIF acetabulum	7	12.8	4	2.7	2.7
ORIF pelvis	10	10		3.5	1.5
ORIF pelvis	7	14.5	7	8	2
Tumor resection	12	23	20	10.5	1.1
Control					
Cervical neuroma	12	6.7	0	0.3	2.4
Glioblastoma	7	2.5	0	0.3	2.7
Throat carcinoma	10	12	0	1	1.6
Brain tumor	7.5	3.5	0	1	5.5
Scoliosis	8	10.5	4	1.5	0.7
Chordoma	6	6.2	4	1.7	0.8

Results

Mean blood loss was approximately 4 times greater in the index than in the controls (Tables 1 and 2). There were no side-effects in the subjects during the study.

While the mean vancomycin concentration was somewhat higher in the index at all time-points, the difference between index and controls did not achieve statistical significance (Figure 1). The mean AAUC from 2 to 7 hrs postdosing was 10.1 mg/L (95% CI 7.9–12 mg/L) for index patients, and 13 mg/L for controls (95% CI 9.3–167 mg/L). In addition, the vancomycin elimination half-lives were similar in index patients (4.9 hrs, 95% CI 3.3–6.4 hrs) and controls (4.6 hrs, 95% CI 3.4–5.7 hrs). Notably, vancomycin concentrations remained at least eightfold higher than the minimum inhibitory concentration for *S. aureus* (0.5 mg/L) 7 or more hours in all but one patient. The low-

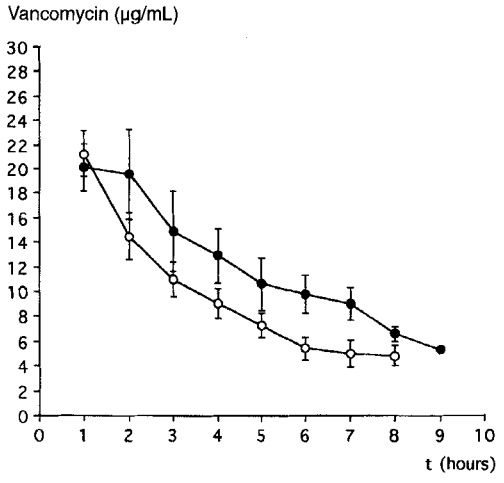

Figure 1.A. Actual serum vancomycin concentrations among patients with high (greater than 2 L, open circles), as compared to low (less than 2 L, closed circles) blood loss.

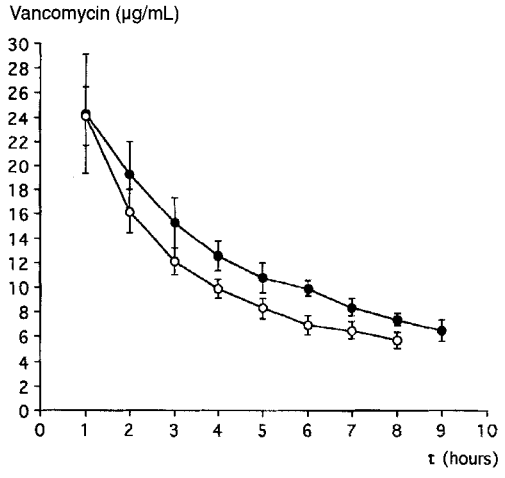

Figure 1.B. Corrected serum vancomycin concentrations among the same patients. The mean ± SEM at each time-point is shown.

est serum vancomycin concentration at any time-point was 3.3 mg/L, this at 7 hours in a 110 kg patient with an estimated blood loss of 11 L.

In this study, all patients received 1 g of vancomycin regardless of body weight. However, individualizing dosages based on body weight may yield different findings. To determine predicted vancomycin concentrations had dosages been adjusted for body weight, the following formula was used: corrected vancomycin concentration = (observed vancomycin concentration × body weight in kilograms) – 70. For example, if a 110 kg patient received 1 g of vancomycin and had a measured vancomycin concentration of 20 mg/L, this corrected vancomycin concentration would have been 32 mg/L if the patient received a weight-adjusted dose of 1.6 g. As shown in Figure 2, the corrected concentration difference between index and controls was statistically significant only at the 6-hour time-point ($p = 0.01$), but at no time before or after, suggesting that this may have been an artifact of multiple comparisons. The lowest corrected serum vancomycin concentration at any time-point was 4.5 mg/L. This was at 8 hours in a 56-year-old, 80 kg patient with a creatinine clearance of 93 mL/min who had an estimated blood loss of 3.5 L.

To characterize further the relationship between blood loss and vancomycin pharmacokinetics, the correlation between absolute blood loss and serum half-life was determined. There was a modest inverse correlation between volume of blood loss and vancomycin half-life ($r = -0.59$, $p = 0.03$) (Figure 2). The 2 patients with massive blood loss had the shortest vancomycin half-lives.

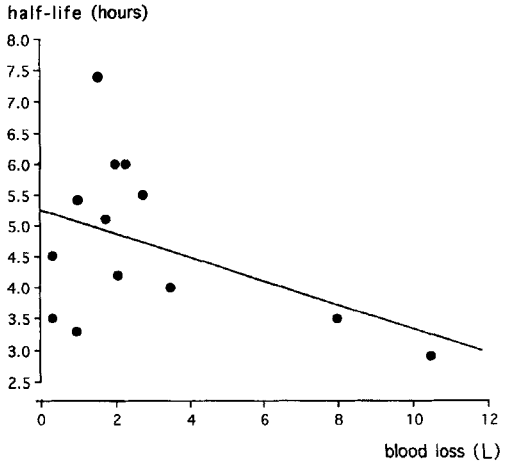

Figure 2. Relationship between total blood loss and vancomycin half-life for all 13 patients. The best-fit line is shown.

Discussion

The question often arises as to whether it is necessary to redose vancomycin during prolonged orthopedic procedures to maintain adequate drug concentrations. Our findings indicate that redosing of vancomycin is seldom indicated, even during prolonged surgical procedures with large volume shifts. Recent well-controlled studies of surgical prophylaxis with cefazolin similarly demonstrated minimal effects of blood loss on drug concentrations during hip arthroplasty and spine fusion procedures (Meter et al. 1996, Polly et al. 1996). However, the operative times and volumes of blood lost were considerably less than in our study.

Vancomycin is safe and efficacious for use in surgical wound prophylaxis. In a randomized prospective study, Maki et al. (1992) found that vancomycin was better than cefazolin and cefamandole for surgical wound infection prophylaxis in vascular and cardiac procedures. Ritter et al. (1989) found a single preoperative dose of vancomycin to be more safe and cost-effective than cephalosporins in 201 consecutive total hip arthroplasties. Previous studies have demonstrated adequate bone and soft tissue penetration in orthopedic procedures (Massias et al. 1992, Scuderi et al. 1993, Guiboux et al. 1995).

The Centers for Disease Control and Prevention recently published guidelines for prudent use of vancomycin in surgical wound prophylaxis, the goal being to prevent the emergence and spread of vancomycin-resistant organisms (Centers for Disease Control 1994). It is suggested that vancomycin be used only for prophylaxis during major surgical procedures involving implantation of prosthetic material or devices at institutions with high rates of methicillin-resistant staphylococcal infections, and should be redosed at 6 hours, regardless of blood loss. Others have suggested a loading dose be given, followed by redosing every 6 hours (Scuderi et al. 1993). In our study, the average length of procedure was 8.4 hours, and the mean serum vancomycin concentration at procedure completion was approximately 6 mg/L, well above the concentrations required to inhibit growth of staphylococci. Administering vancomycin every 8 or 12 hrs would seem appropriate for most patients. More frequent dosing might be indicated for younger patients who eliminate vancomycin more rapidly, but this issue was not addressed by our study. In addition, while adjusting vancomycin dosage based on total body weight, appears to have little impact on clinically relevant intraoperative vancomycin concentrations, giving 1.5 g of vancomycin to patients weighing more than 90 kg may be warranted, particularly those with anticipated large volume blood loss who are undergoing procedures exceeding 8 hours.

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Centers for Disease Control and Prevention MMWR. Recommendations for preventing the spread of vancomycin resistance. Recommendations of the Hospital Infection Control Practices Advisory Committee 1994; 44 (RR-12): 1-12.

Cockcroft D W, Gault, M H. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.

Fitzgerald R H, Washington J A. Contamination of the operative wound. Orthop Clin North Am 1975; 6: 1105-14.

Guiboux J P, Cantor J B, Small S D. The effect of prophylactic antibiotics on iatrogenic intervertebral disc infections: A rabbit model. Spine 1995; 20: 685-8.

James P J, Butcher I A, Gardner E R. Methicillin-resistant Staphylococcus epidermidis in infection of hip arthroplasties. J Bone Joint Surg (Br) 1994; 76: 725-7.

Johnson K D, Johnston D W C. Orthopedic experience with methicillin-resistant Staphylococcus aureus during a hospital epidemic. Clin Orthop 1986; 212: 281-4.

Mader J T, Cierny G III. The principles of the use of preventive antibiotics. Clin Orthop 1984; 190: 75-82.

Maki D G, Bohn M J, Stolz S M. Comparative study of cefazolin, cefamandole and vancomycin for surgical prophylaxis in cardiac and vascular operations: A double-blind randomized trial. J Thorac Cardiovasc Surg 1992; 104: 1423-34.

Massias L, Dubois C, de Lentdecker P, Brodaty O:. Penetration of vancomycin in uninfected sternal bone. Antimicrob Agents Chemother 1992; 36: 2539-41.

Meter J J, Polly D W, Bruekner R P, et al. Effect of intraoperative blood loss on the serum level of cefazolin in patients managed with total hip arthroplasty. J Bone Joint Surg (Am) 1996; 78 (8): 1201-5.

Polly D W, Meter J J Bruekner R, et al. The effect of intraoperative blood loss on serum cefazolin level in patients undergoing instrumented spinal fusion–a prospective, controlled study. Spine 1996; 21 (20): 2363-7.

Ritter M A, Barzilauskas C D, Faris P M. Vancomycin prophylaxis and elective total joint arthroplasty. Orthopedics 1989; 12: 1333-6.

Scuderi G J, Greenberg S S, Banovac K, Martinez O V, Eismont F J. Penetration of glycopeptide antibiotics in nucleus pulposus. Spine 1993; 18: 2039-42.