The Comparative Influence of Prophylactic Antibiotics on the Prothrombin Response to Warfarin in the Postoperative Prosthetic Cardiac Valve Patient

Cefamandole, Cefazolin, Vancomycin

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A prospective randomized trial was conducted comparing the effect of three antibiotics: cefamandole (CM), cefazolin (CZ), and vancomycin (V), used as prophylaxis for prosthetic valve surgery, on the prothrombin (PT) response to warfarin (W) on the third day of anticoagulant therapy. Twenty patients, with normal preoperative PTs, were randomized to each antibiotic. Their PTs were not significantly different at 2 hours after operation and the morning before W was begun. The three groups received similar W doses for 2 days, and the PT, as percentage of activity, on the morning of the third day demonstrated that V (51 ± 18%) was significantly greater ($p < 0.005$) than CM (29 ± 14%) or CZ (38 ± 18%). CM had a significantly greater percentage of change in PT (64 ± 14%, $p < 0.0001$) from the first to third day than either CZ (51.1 ± 18%) or V (44.6 ± 19%). CM also had a greater number of patients (6) with PTs ≥ 30 seconds on day 3 than either CZ (1) or V (1). The antibiotic influence on the PT response to W in this study is ranked as CM > CZ > V.

THE FIRST-GENERATION cephalosporins (*e.g.*, cephalothin, cefazolin) have been widely used as the antibiotic of choice for prophylaxis of surgical infections. These antibiotics have been reported to cause hypoprothrombinemia in patients receiving long-term antibiotic therapy with a poor dietary intake or in renal failure.[1-3] More recently, the second-generation cephalosporins, such as cefamandole, have enjoyed wide popularity in prophylaxis of heart surgery because of their extended gram-negative spectrum and activity against *Staphylococcus aureus* and *Staphylococcus epidermidis*. Cefamandole contains the 1-N-methyl-5-thiotetrazole (MTT) group that has been implicated as a cause of accelerated prothrombin (PT) depletion associated with episodes of both major and minor bleeding.[4,5] Vancomycin, a noncephalosporin antibiotic with only a gram-positive spectrum, has not been implicated as a cause of hypoprothrombinemia.[6]

For patients who have prosthetic valve replacement surgery, adequate anticoagulation is of vital importance in prevention of thromboembolic complications. The type of prophylactic antibiotic administered to these patients during and after surgery could influence the response to subsequent warfarin anticoagulation therapy.

We have reported a retrospective investigation comparing the PT response to warfarin in patients undergoing prosthetic valve surgery who received either cefamandole or vancomycin. This study indicated that patients receiving cefamandole had a significantly greater hypoprothrombinemic response after the first 2 days of warfarin therapy when compared with patients administered vancomycin.[7]

To confirm this retrospective work, we conducted the following prospective randomized, open-label trial comparing the effect of cefamandole, cefazolin, and vancomycin as prophylactic antibiotics on the PT response to warfarin in patients who had prosthetic valve surgery.

Methods

Sixty patients who were scheduled to have cardiac valve replacement surgery were prospectively assessed and randomly assigned by a random number table to receive either cefamandole, cefazolin, or vancomycin for surgical prophylaxis. All patients with a history of either a penicillin or cephalosporin allergy were assigned to receive vancomycin. The study was approved by the

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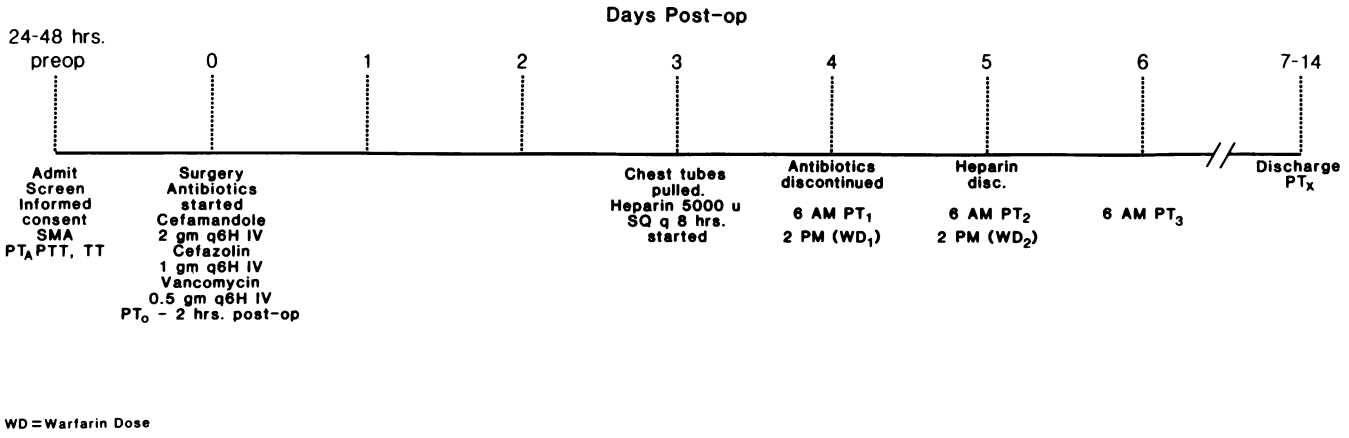

FIG. 1. The typical hospital course for a prosthetic valve patient.

Institutional Review Board and informed consent was obtained the day before surgery.

Preoperative exclusion criteria were: (1) PT 2 seconds greater than control, platelets < 150,000 cells/μL, PTT greater than normal, thromboplastin time (TT) 2 seconds greater than control; (2) a history of active liver disease; (3) a serum creatinine level of >2 mg/dL, BUN > 40 mg/dL; and (4) emergent surgery due to rapidly worsening heart failure or bacterial endocarditis.

Patients were excluded in the postoperative period if they: (1) had a serum creatinine level of >2 mg/dL, BUN > 40 mg/dL; (2) experienced prolonged cardiovascular instability requiring vasopressors, vasodilators, intravenous inotropes, and/or intra-aortic balloon pump for more than 48 hours after operation; and (3) had liver impairment or hepatitis.

One team of five cardiovascular surgeons following a uniform protocol performed all surgeries in a single hospital. Surgical data were obtained from the anesthesia record, cardiopulmonary bypass record, and the operative reports. All patients received identical anesthetic agents, including pancuronium, fentanyl, ketamine, enflurane, and diazepam. A St. Jude's medical cardiac valve prosthesis was used in all patients. Cardiac pulmonary bypass was accomplished using moderate systemic hypothermia (28 C) and cold potassium cardioplegia. Cefamandole, 2 g, cefazolin, 1 g, or vancomycin, 0.5 g, were administered intravenously as the prophylactic antibiotic before the chest incision and every 6 hours up to 24 hours after chest tube removal.

The typical hospital course of these patients including surgery and postoperative recovery is outlined in Figure 1. Warfarin was the only oral anticoagulant used and administered at 2:00 P.M. each day. The PT was measured: on admission 24–48 hours before operation (PT_A); after operation immediately on return to the intensive care unit (PT_O); at 6:00 A.M. the beginning day of warfarin therapy (PT_1); and daily throughout the hospital stay. Warfarin therapy and dosage selection was at the discretion of the attending cardiologist and adjusted with a PT goal of 1.5–2 times control. The initial warfarin dose was 10 mg in 67% of patients. A PT was also obtained daily for 2 or 3 consecutive days (PT_B) between PT_O and PT_1 in nine patients who received cefamandole, in nine patients who received cefazolin, and in 12 patients who received vancomycin. The PT per cent change (PT%C) was computed by $PT_1\%A - PT_3\%A / PT_1\%A \times 100$.

The PT was measured by the Quick method using a Dade Thromboplastin-C reagent and processed using an MLA Electra-700 automatic coagulation timer (American Scientific Products, McGaw Park, IL) with a coefficient of variation (CV) of 1.8% at normal control and 4% CV at high control. The percentage of prothrombin activity (PT%A) was obtained by converting the PT in seconds to percentage activity by means of a calibration curve obtained from the laboratory. This relationship between PT seconds and PT%A is nonlinear as seen in Figure 2.

Warfarin plasma concentrations were determined by a reverse-phase, high-performance liquid chromatography (HPLC). Warfarin and the internal standard, p-chloro-warfarin, were extracted from acidified, citrated plasma with cyclopentane. The organic layer was evaporated and the residue was reconstituted with 200 μL of mobile phase consisting of 57% acetonitrile/43% water, pH 3.0. An aliquot was injected onto a DuPont Zorbax® C column (E. I. duPont de Nemours and Co., Inc., Wilmington, DE) and the effluent was monitored at 280 nm with a Waters® 440 absorbance detector (Millipore, Waters Chromatography Division, Milford, MA). Concentrations were directly proportional to the absorbance, and as little as 0.1 μg/mL warfarin could be detected in 200 μL of plasma. The assay was linear from

0.1 to 10.0 μg/mL with an absolute recovery greater than 80%. Intra-day assay CV ranged from 2.2 to 11.1% over a concentration range from 0.1 to 10.0 μg/mL. Standards assayed over a 6-month period had CVs ranging from 0.5 to 14.5%.[8]

Patients were assigned to a New York Heart Association (NYHA) functional class using the standard published criteria.[9]

The ANOVA with the Neuman–Keuls multiple range test was used to compare the means of the three groups, and linear regression was used for statistical evaluation of the data. Unless otherwise stated, all data are reported as the mean ± SD. Statistical significance was designated at the $p \leq 0.05$ level.

Results

The demographic data describing the three groups as listed in Table 1 indicate the groups were well matched for sex and type of surgery. The patients who received cefamandole and cefazolin were significantly older than those receiving vancomycin. The NYHA classification of cardiovascular status was similar for the three groups, with the majority (70%) in Class III. Some of the more important parameters that were assessed and not found to be significantly different among the three groups are: (1) sex, (2) PT_A, (3) PT_O, (4) time on cardiopulmonary bypass, (5) length of surgery, (6) time of anesthesia, (7) total blood loss during and 24 hours after surgery, and (8) serum albumin level.

Five patients received potentially interacting drugs in the postoperative period. They were cefamandole (2 patients: 1 quinidine, 1 cimetidine), cefazolin (1 patient: cimetidine), and vancomycin (2 patients: 1 quinidine and 1 cimetidine). Quinidine and cimetidine may potentiate the effects of warfarin.[10] Removing these patients from their respective groups did not alter any of the statistical values; therefore, they are included in all the reported results.

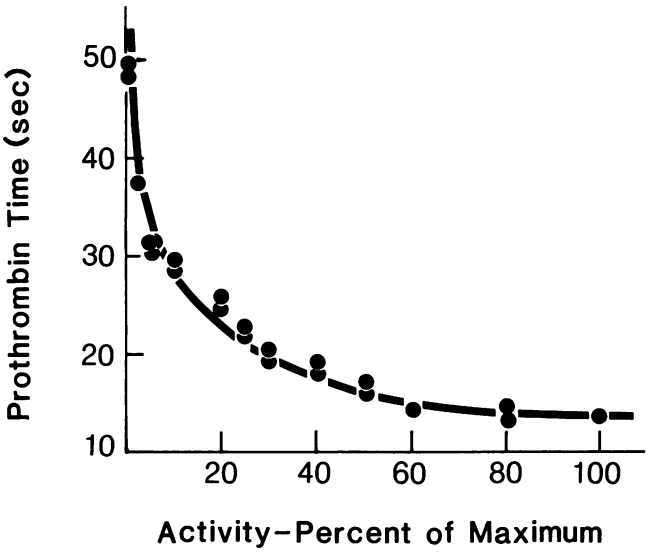

FIG. 2. Prothrombin percent activity: second relationship. The relationship between per cent activity and the prothrombin time in seconds is curve linear on a linear–linear scale.

TABLE 1. *Demographic Data for 60 Prosthetic Valve Patients*

	Cefamandole N = 20	Cefazolin N = 20	Vancomycin N = 20
Sex M/F	10/10	14/6	12/8
Age (years)	64.3 ± 13§	62 ± 9.5§	56 ± 10.5
Type of surgery			
CAB with AVR	2	5	4
CAB with MVR	3	2	3
AVR	11	7	9
MVR	3	5	4
AVR with MVR	1	0	0
CAB with AVR and MVR	0	1	0
NYHA class			
I	0	1	1
II	3	5	2
III	15	12	15
IV	2	2	2
PT_A* (%A)†	88.4 ± 9.3	88.3 ± 11.3	90.3 ± 8.5
PT_O‡ (%A)	52 ± 4.0	54 ± 3.6	51 ± 4.1
Time of bypass (min)	105 ± 46	107.3 ± 41	113 ± 70
Length of surgery (min)	203 ± 112	210.7 ± 56	210.9 ± 108
Anesthesia time (min)	308 ± 159	283 ± 65	384.8 ± 130
Blood loss during surgery (ML)	1038 ± 814	1022 ± 680	1069 ± 1152
Preoperative albumin (g/dL)	3.8 ± 0.3	3.8 ± 0.4	4.2 ± 0.4

* PT_A = admission 24–48 hours before operation.
† (%A) = percent prothrombin activity.
‡ PT_O = 2 hours after operation.
§ Cefamandole, cefazolin > vancomycin, $p < 0.05$.
CAB = coronary artery bypass.
AVR = aortic valve replacement.
MVR = mitral valve replacement.

TABLE 2. *The Prothrombin Percent Activity (PT%A), Warfarin Doses, and Serum Levels for the 60 Prosthetic Valve Surgery Patients*

	Cefamandole N = 20	Cefazolin N = 20	Vancomycin N = 20
PT_1 (%A)*	80 ± 18	82 ± 12	90 ± 12
PT_3 (%A)†	29 ± 14#	38 ± 18#	51 ± 18
PT%C‡	64 ± 14.4**	51.1 ± 18	44.6 ± 19
WD_1 (mg)§	9 ± 2	8.9 ± 3	9.8 ± 2
WD_2 (mg)‖	7.4 ± 4	7.8 ± 2	9.1 ± 2
W (μ/mL) PT_3¶	0.85 ± 0.4	0.87 ± 0.36	1.02 ± 0.6
$PT_3 \geq 30$ seconds (N)	6	1	1
$PT_3 \geq 20$ seconds (N)	17	10	5

* PT_1 = baseline PT on 0600 the day warfarin is started.
† PT_3 = 16 hours after second warfarin dose.

$$\ddagger \text{PT\%C} = \frac{PT_1\%A - PT_3\%A}{PT_1\%A} \times 100$$

§ WD_1 = warfarin dose, day one.
‖ WD_2 = warfarin dose, day two.
¶ Warfarin plasma levels obtained with PT_3.
# Cefamandole, cefazolin > vancomycin, $p < 0.05$.
** Cefamandole > cefazolin, vancomycin, $p < 0.01$.

The PT_1%A for the three groups was not significantly different ($p = 0.113$) (Table 2). PT_3%A was significantly lower for cefamandole and cefazolin, when compared with vancomycin, but not from one another. In contrast, the PT%C was significantly greater for cefamandole, compared with cefazolin and vancomycin, which were not significantly different. The first warfarin dose was ≥10 mg in 80% of patients receiving cefamandole, in 55% of patients receiving cefazolin, and in 85% of patients receiving vancomycin with the mean dose for each of the first two days and total dosage being similar. Warfarin plasma levels obtained with the PT_3 sample were not significantly different among the three groups. Cefamandole had a greater number of patients with PTs greater than both 20 and 30 seconds at PT_3 than the other two antibiotic groups.

The other identifiable difference between the three antibiotic groups was the relationship between the duration of postoperative prophylactic antibiotic therapy and the PT_1%A. Because the commencement of warfarin therapy was not controlled during this study, Table 3 lists the numbers of patients in each group who were receiving antibiotics concurrently when either PT_1, PT_2, or PT_3 was obtained. A linear regression using only those patients receiving antibiotics concurrent with the PT_1 sample compared the duration of antibiotics with the PT_1%A and indicated a moderate negative correlation for the cefamandole group ($R = -0.52$, $p = 0.05$) (Fig. 3), but not for cefazolin ($R = -0.16$, $p = 0.53$) or the vancomycin group ($R = -0.08$, $p = 0.82$). The mean duration of antibiotic therapy up to PT_1 was not significantly different among the three groups ($p = 0.12$).

TABLE 3. *The Number of Patients Receiving Concurrent Antibiotic Administration During the Time PT Samples Were Obtained and Average Duration of Antibiotic Therapy Until PT_1*

	Cefamandole N = 20	Cefazolin N = 20	Vancomycin N = 20
PT_1	15 (75)*	19 (95)	12 (60)
PT_2	14 (70)	11 (55)	8 (40)
PT_3	2 (10)	5 (25)	1 (5)
Therapy until PT_1 (days)†	4.6 ± 1.6	4.1 ± 0.8	3.8 ± 1.2

* N (% of total patients).
† Average number of days of antibiotic therapy until PT_1 obtained.

All of the PT_B%A values were greater than the patients' own PT_O%A. At least one of the PT_B%A values was equal or lower than the patients' PT_A%A in seven of nine patients (78%) who received cefamandole, in two of nine patients (22%) who received cefazolin, and in one of 12 patients (8%) who received vancomycin.

No bleeding episodes requiring transfusion were observed for the 60 patients. No apparent differences in outcome were associated with the three antibiotic groups and associated warfarin therapy.

Discussion

This prospective study reconfirms our previous retrospective report that patients receiving cefamandole, as a prophylactic antibiotic, had a greater hypoprothrombinemic response to warfarin than similar patients receiving vancomycin in the early postoperative period after prosthetic valve replacement. We reported previously that 14 of 44 patients (32%) receiving cefamandole and one of 16 patients (6%) receiving vancomycin had a $PT_3 > 32$ seconds, 16 hours after the second warfarin dose.[7] This is comparable to four of 20 (20%), 0 of 20, and 0 of 20 patients receiving cefamandole, cefazolin, and vancomycin, respectively, with a $PT_3 \geq 32$ seconds in the current study.

Although the PT%C supported a greater hypoprothrombinemia effect of cefamandole compared with cefazolin and vancomycin, we were surprised that the mean PT_3%A data were unable to differentiate statistically between cefamandole and cefazolin. This could be a result of too small of a sample size. The recent literature provides a possible explanation, but first we should review the three reported mechanisms of cephalosporin-induced hypoprothrombinemia.

The commonly cited mechanisms are[11]: (1) alteration of the bacterial bowel flora, with the suppression of vitamin K_1 production, (2) an inhibition of the carboxylation process necessary for the transformation of the procoagulant factors II, VII, IX, X to their active forms,

and (3) the inhibition of vitamin K 2,3-epoxide reductase, which interferes with Vitamin K_1 activity.

The role of bowel flora in vitamin K production and its importance in maintaining a normal PT in humans is a subject of some dispute.[11] Most episodes of hypoprothrombinemia attributed to this mechanism have involved long-term, multiple antibiotic usage in seriously ill, malnourished, and potentially vitamin K-depleted patients or those with renal failure.[12] Our patients were not in renal failure; however, Blackburn et al. did report a 53% incidence of malnutrition in patients with a primary cardiac diagnosis. A subsample of 14 patients with valvular disease in NYHA Class III and IV were found to have a decreased weight/height index, skinfold thickness, and muscular circumference. Their patients' albumin levels, like ours, were generally within normal limits, but 10 of 14 patients tested negative for cell-mediated immunity.[13] We did not conduct a sophisticated nutrition assessment and cannot discount the possibility that an occult vitamin K deficiency existed, even with a normal PT_A before operation.

The pharmacologic basis for mechanisms 2 and 3 center on the MTT side chain found in not only cefamandole and several other cephalosporins (moxalactam, cefoperazone, cefotetan). Cephalosporins with the MTT side chain have been reported to cause hypoprothrombinemia more quickly and with greater frequency than non-MTT containing cephalosporins.[11] Lipsky reported that MTT inhibited gamma-carboxylation in a microsomal preparation prepared from rat livers.[14] Utolia and Suttie demonstrated that this inhibition was not due to the parent compound by reporting that cefamandole and structural analogs required much larger, and not clinically relevant, concentrations to produce 50% inhibition of the vitamin K-dependent carboxylase system.[15]

Vitamin K_1 2,3-epoxide reductase is found in the liver microsomes and reduces the vitamin K epoxide, formed from vitamin K_1 by carboxylase, back to the quinone or hydroquinone. Inhibition of vitamin K metabolism at the epoxide reductase step blocks the utilization of this vitamin. Bechtold et al. measured serum concentrations of vitamin K_1 2,3-epoxide, after giving 10 mg of vitamin K_1 intravenously in patients experiencing moxalactam- or cefamandole-induced hypoprothrombinemia. This metabolite is only measurable when vitamin K_1 is given in the presence of epoxide reductase inhibitors, such as coumarins or salicylates, and provides some inferential evidence that cefamandole has a coumarin-like action.[16]

None of the previous discussion would seem to support the possibility that cefazolin should have an additive hypoprothrombinemic effect with warfarin in our patient population. Kerremans et al. reported *in vitro* evidence that not only did MTT inhibit gamma-carboxylation but that MTD (2-methyl-1,3,4-thiadiazole-5-thiol), found in cefazolin, also had a similar effect.[17] They also demonstrated that the carboxylation inhibitory activity of both MTT and MTD was attenuated by methylation. Furthermore, MTD was a better substrate than MTT for both methylation enzymes: (1) thiopurine methyltransferase located in the kidney, and (2) thiomethyl transferase located in the liver. This could infer that MTD does not cause the same degree of hypoprothrombinemia because of rapid inactivation. However, MTD formation from cefazolin has not been demonstrated *in vivo*.[17]

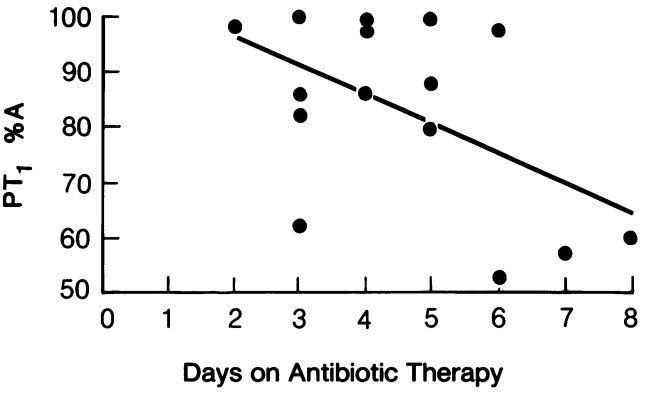

FIG. 3. The relationship between the duration of cefamandole administration and prothrombin per cent activity. The relationship between the double/double duration of prophylactic cefamandole therapy and the prothrombin time per cent activity on the morning that warfarin therapy was begun ($R = -0.52$, $p = 0.05$), indicating that as duration increased prothrombin activity declined.

Hypothermic cardiopulmonary bypass has influence on the entire clotting system. The vitamin K-dependent coagulation factors (II, VII, IX, X) have been reported to be depressed from 46% to 62% of preoperative values immediately after bypass.[18] This is consistent with our PT_O%A given in Table 1. Mori et al. measured the PT before operation and daily for 2 weeks after bypass surgery and reported that in only the first postoperative day PT, in seconds, was significantly greater than the preoperative PT. All PT values were within normal limits but the prophylactic antibiotic and its regimen were not specified.[19] A limited number of our patients in each group had two or three PT_B obtained and indicated a spontaneous recovery toward normal from the PT_O during the first 3–5 postoperative days. There is some hint that this return toward normal was inhibited in the cefamandole group by having more patients with a PT_B%A equal or less than their respective PT_A%A. In addition, there was a moderate correlation between an increasing duration of cefamandole therapy and decreased PT_1%A.

Although we did not attempt to quantitate the oral vitamin K intake of our patients after operation, the

usual impression is that MTT-induced hypoprothrombinemia is quickly and easily reversed in a matter of hours by vitamin K administration.[11] This has not been universally true as Hooper et al.[5] and Fainstein et al.[20] reported. Lipsky provides experimental evidence that this MTT-induced hypoprothrombinemia may not be just a vitamin K inhibition problem because vitamin K_1 failed to reverse *in vitro* MTT inhibition of gamma-carboxylation after the reaction had started.[21] This may partially explain the low PT_1%A values that were noted in the cefamandole and cefazolin groups despite some oral food intake.

Yacobi et al. reported that 31 cardiovascular patients had total warfarin plasma levels of 0.4–3.27 μg/mL associated with a PT range of 15.6–29.8 seconds.[22] The warfarin plasma levels we obtained measured only the total racemic compound and were not at a steady state. Even so, they indicate that warfarin absorption took place, achieved similar concentrations, and are consistent with previous reported therapeutic concentrations in all three antibiotic groups.

The PT response to warfarin is influenced by many factors such as age, diet, congestive heart failure, or drug interactions to list a few. Sawyer et al. recently reported that age had a negative correlation with warfarin dosage requirements. This study included outpatients and a wider range of ages (19–91 years) than our patients.[23] The possible influence of the vancomycin group being 6–8 years younger on the PT response to warfarin in this setting is unknown. Yacobi et al. could find no rank order correlation between the average PT and average warfarin dose, total warfarin concentration, or free warfarin concentration.[22] The "normal" response to warfarin in the early postoperative phase in patients who had prosthetic valve replacement has not been rigorously documented to our knowledge; therefore, we cannot discount some other explanation for the observed differences among the three antibiotics. The consistent difference in PT response between cefamandole and vancomycin in this and our previous report, involving a total of 100 patients, supports a drug-induced effect.

The exact mechanism for the greater PT%C associated with the cefamandole group compared with cefazolin and vancomycin is unknown, but could possibly be due to the presence of MTT when the first warfarin doses were administered. The pharmacokinetics of MTT in this setting have not been reported and it is only recently that Aronoff et al. reported MTT disposition in a group of normal patients and in patients with anuric renal failure after a single intravenous dose of cefamandole. The patients with renal failure had a 10-fold increase in cefamandole half-life, and the MTT area under the curve was 50 times that seen in normals.[24] The importance of this is to the development of hypoprothrombinemia, or interaction with warfarin requires further study.

The possibility that the dosage regimens used for cefamandole and cefazolin were of unequal "PT suppression" potency cannot be discounted. We did not measure serum concentrations of either drug. Utolia and Suttie reported that cefamandole concentrations 10 times those observed after 2 g administered intravenously were needed to inhibit the vitamin K-dependent carboxylase system by 50%.[15] We were unable to find comparable data for cefazolin. Therefore, serum measurements of both parent compounds plus MTT and MTD would have to be done in an attempt to determine the relative "PT suppression" potency of these two cephalosporins.

Conclusion

This prospective study reconfirms our previous retrospective report that cefamandole can have an additive effect to warfarin in producing hypoprothrombinemia in the prosthetic heart valve patient. The study further provides evidence that cefazolin may have a similar, but intermediate, effect between cefamandole and vancomycin. Although none of our patients had an adverse reaction from this exaggerated hypoprothrombinemic response, we still recommend a baseline PT and caution before administering warfarin to patients receiving either cefamandole or cefazolin. The exact mechanism for this exaggerated hypoprothrombinemic response to warfarin after the administration of cefamandole or cefazolin is not completely understood but may be related to the MTT or MTD side chain and its influence on either gamma-carboxylation and/or vitamin K_1 2,3-epoxide reductase.

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