The Influence of Prophylactic Antibiotics on the Warfarin Anticoagulation Response in the Postoperative Prosthetic Cardiac Valve Patient

Cefamandole versus *Vancomycin*

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The influence of cefamandole and vancomycin used for prophylaxis on the warfarin anticoagulation response in 60 cardiac valve replacement patients during the postoperative period is presented. Patients were divided into two groups, hyper-responders prothrombin time (PT) ≥ 32 sec, 48 hr after the initial warfarin dose (GrI_{HR}), or normal responders PT < 32 sec ($GrII_{NR}$). Fifteen patients (25%) were in GrI_{HR} (PT 44.3 ± 10.5) and 45 in $GrII_{NR}$ (21 ± 5). Fourteen of the 15 GrI_{HR} patients received cefamandole and 1 of the 15 GrI_{HR} patients received vancomycin $p < 0.05$, as prophylaxis. Warfarin sensitivity was assessed using a warfarin dose index (WDI) calculated in the initial postoperative period (WDI_{INT}) and at discharge (WDI_{DIS}). GrI_{HR} patients had greater WDI_{INT} and WDI_{DIS} compared to $GrII_{NR}$ $p < 0.001$. Baseline prothrombin time measured 8 hours prior to start of warfarin therapy (PT_{BL}), was linearly correlated to the WDI_{INT} with $r = 0.8$, $p < 0.001$ in cefamandole patients only. The data suggests that cefamandole increases warfarin sensitivity early in the postoperative course of oral anticoagulation therapy, which may lead to excessively high prothrombin times with the possibility for serious bleeding.

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 who have a poor dietary intake, or who are in renal failure.[1-3]

Recent incidents of hypoprothrombinemia secondary to cefamandole (a second generation cephalosporin) with major and minor episodes of bleeding have been reported in patients on parenteral nutrition or restricted diets after surgery.[4,5]

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

Our study reported here stemmed from two cases of unusually high prothrombin times (PT) of 50 and 62 seconds with one patient bleeding from his I.V. sites, occurring within 48 hours of an initial 10-mg dose of warfarin.

Because of these incidents, the response to warfarin anticoagulant therapy was studied retrospectively in 60 cardiac valve replacement patients receiving cefamandole or vancomycin prophylaxis during and after surgery.

Patients and Methods

Seventy-one patients who had undergone cardiac valve replacement surgery were retrospectively reviewed for their response to postoperative warfarin anticoagulation therapy. One team of four surgeons following a uniform protocol (before, during, and after surgery) performed all of the surgery in two hospitals: United Hospitals, Inc. (UHI) and Abbott-Northwestern Hospital (A-NW).

All patients undergoing cardiac valve replacement surgery at UHI from June 1980 to May 1981 were reviewed. Of the 64 patients reviewed, 54 patients were included in the study. The remaining 10 patients were excluded

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TABLE 1. *Demographic Data (Sex and Surgery) for 60 Prosthetic Valve Patients*

	Number of Patients	Percentage
A. Sex		
Male	38	63%
Female	22	37%
B. Type of Surgery		
Aortic valve replacement (AVR)	21	35%
Mitral valve replacement (MVR)	16	26%
Coronary artery bypass (CAB) with MVR	10	17%
CAB with AVR	9	15%
AVR with MVR	4	7%

TABLE 2. *List of Drugs Potentially Interacting with Warfarin Given in the Postoperative Course of Anticoagulation Therapy*

Drugs	Number of Patients
Quinidine sulfate	14
Cimetidine	4
Chloral Hydrate	2
Indomethacin	2
Chlorothalidone	1
Amiodarone	1
Synthroid	1
Sufinpyrazone	1

because two had received no warfarin, two had other procedures concomitantly with their surgery, five patients died, and one patient had a prior history of hepatitis. None of the patients were known alcoholics, had significant liver disease or renal disease, were in uncompensated heart failure, or were in a hypermetabolic or malabsorptive state. Forty-four of the 54 patients studied were given cefamandole as the prophylactic antibiotic and 10 of the patients received vancomycin as the prophylactic antibiotic due to a penicillin allergy. Seven other penicillin allergic patients undergoing cardiac valve replacement surgery at A-NW from June 1980 to August 1981 were reviewed in a random manner. One patient was excluded from this group because no warfarin was given, leaving 16 vancomycin patients in the study.

A total of 60 surgical patients (44 on cefamandole and 16 on vancomycin) were analyzed (Table 1). The patient's past medical history, medication on admission to the hospital, and drugs administered during the course of warfarin therapy were recorded. Every patient had a serum sodium, potassium, BUN, total protein, albumin, total bilirubin, creatinine, calcium, uric acid, alkaline phosphatase, SGOT, LDH, and a cholesterol study done. In addition, prothrombin time, activated partial thromboplastin time, thrombin time and platelets, were measured before surgery for each of the patients.

The prothrombin time was measured by the Quick Method using a Dade Thromboplastin-C reagent. The percentage of prothrombin activity was obtained by converting the PT to percentage activity by means of a calibration curve from the laboratory.

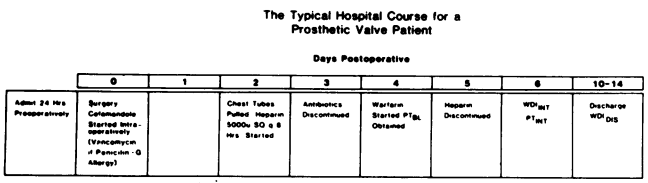

FIG. 1. PT_{BL} baseline prothrombin time, PT_{INT} initial prothrombin time, WDI_{INT} initial warfarin dose index, WDI_{DIS} discharge warfarin dose index.

Surgical data was obtained from the anesthesia record, cardiopulmonary bypass data, and the operative reports. All the 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. Surgical techniques and cardiopulmonary bypass procedures were the same in all patients with a moderate (28 C.) systemic hypothermia and cold potassium cardioplegia. Either I.V. cefamandole (2 gm) or vancomycin (500 mg) were administered as the prophylactic antibiotic before the chest incision and every 6 hours thereafter up to 24 hours following chest tube removal (average 72 hours).

The typical hospital course, including surgery and postoperative recovery of these patients, is outlined in figure 1. Warfarin was the only oral anticoagulant used. Prothrombin times were measured daily throughout the course of warfarin therapy. To measure warfarin sensitivity, the warfarin dose index (WDI) was calculated 48 hours after the initial warfarin dose (WDI_{INT}),* and at discharge (WDI_{DIS})** for each patient (Fig. 1).

$$\text{WDI (sec/mg/kg)} = \left(\frac{PT_{patient} - PT_{control}\ (sec)}{\dfrac{\text{cumulative warfarin dose (mg) during preceding 2* or 4** days}}{\text{actual body weight (kg)}}} \right)$$

A safe, therapeutic range for hypocoagulability using Dade thromboplastin-C is a PT between 1½ to 2½ times that of the control. In this study, patients having a PT two days after the initial warfarin dose (PT_{INT}) > 32 secs (*i.e.*, > 2½ control) or having a $WDI_{INT} \geq 90$ secs/mg/kg (*i.e.*, ≥ 1 S.D. of the mean WDI_{INT} of all patients) were included in Group I "Hyper-responders," (GrI_{HR}). The remaining patients were included in Group II "Normal Responders," ($GrII_{NR}$). The WDI data was further divided into two additional subsets: *Uncorrected* subgroup, consisting of all patients without concern for potential

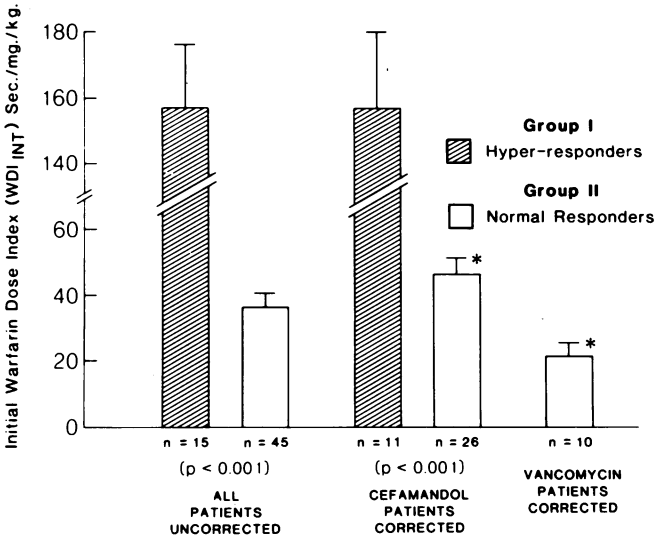

FIG. 2. The mean initial warfarin dose index (WDI_{INT}) by patient groups for both antibiotics, uncorrected and corrected for potential drug interactions with warfarin. Vertical bars represent ±S.E.M. *$p < 0.01$.

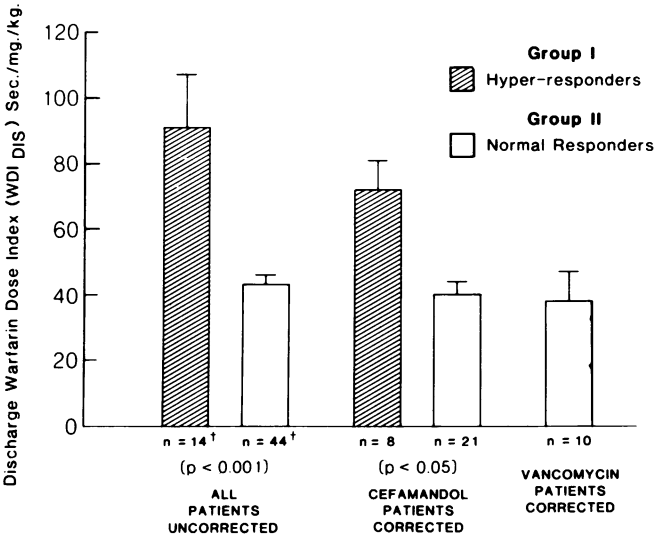

FIG. 3. The mean warfarin dose index at discharge (WDI_{DIS}) by patient groups for both antibiotics uncorrected and corrected for potential drug interactions with warfarin. († one patient was removed from each group because WDI_{DIS} could not be calculated due to a short hospital stay). Vertical bars represent ±S.E.M.

drugs interacting with warfarin, and *corrected* subgroup, consisting only of patients without any potential warfarin drug interactions (Table 2).[6,7]

A Student's two-tailed t-test, linear regression analysis, and a Chi square test were used for statistical evaluation of the data. Unless otherwise stated, all data is reported as the mean ± standard deviation.

Results

Fifteen patients (25%) were classified as hyper-responders out of the 60 patients analyzed. These included 14 of the 44 patients (32%) receiving cefamandole, and 1 of the 16 patients (6%) receiving vancomycin ($p < 0.025$). Correcting for potential drug interactions eliminated the one vancomycin and three cefamandole patients in this group.

In the uncorrected subgroup PT_{int} in GrI_{HR} patients was 44.3 ± 10.5, (range 32.5–62.5 seconds), and in $GrII_{NR}$ the patients mean was 21 ± 5 (range 12.3–31.8 seconds) $p < 0.001$. In the corrected subgroup, mean PT_{int} for both GrI_{HR} and $GrII_{NR}$ remained unchanged.

A warfarin sensitivity index was calculated and both the WDI_{INT} and WDI_{DIS} were significantly greater for GrI_{HR} than $GrII_{NR}$ $p < 0.001$. Within $GrII_{NR}$, cefamandole patients were initially more sensitive to warfarin (higher WDI_{INT}), compared to the vancomycin patients $p < 0.001$ (Figs. 2 and 3).

Six GrI_{HR} patients were given fresh frozen plasma, vitamin K, or both for an elevated PT_{INT}. All responded with a decrease in their PT. However, they had a mean WDI_{DIS} identical to those not similarly treated within the group.

The cumulative warfarin dose administered to the vancomycin group of patients before the PT_{INT} was larger than the cumulative dose received by the cefamandole patients (Table 3).

Cefamandole patients in GrI_{HR} were older (67.5 ± 8 years) than $GrII_{NR}$ (59 ± 12 years) $p < 0.005$. Vancomycin patients in $GrII_{NR}$ had a mean age of 62 ± 8 years which was not significantly different from GrI_{HR} cefamandole patients (Table 4).

Twenty-eight patients in the study had a baseline PT, (PT_{BL}) measured 8 hours prior to the beginning warfarin therapy. PT_{BL} was converted to a percentage of prothrombin activity. GrI_{HR} cefamandole patients (n = 5), had a significantly lower percentage of prothrombin activity (56 ± 17%) compared to $GrII_{NR}$ cefamandole patients (n = 14 [81 ± 18%]) and vancomycin patients (n = 9 [94 ± 8% $p < 0.05$]).

TABLE 3. *Total Warfarin Doses (mg) Before* WDI_{INT}

A. Cefamandole patients	17.4 ± 5	N.S.*	
B. Vancomycin patients	20.3 ± 5.3		
	Group I_{HR}		Group II_{NR}
C. All patients	n = 15		n = 45
	15 ± 5	N.S.	19 ± 5
	(7.5–22.5)		(10–30)
Cefamandole patients	n = 14		n = 30
	15 ± 5	N.S.	18.8 ± 5
	(7.5–22.5)		(10–30)
Vancomycin patients	n = 1		n = 15
	12.5		20.8 ± 5
			(15–30)

* N.S. = $p > 0.05$.

TABLE 4. *Age in Years*

	Group I_{HR}		Group II_{NR}
All patients	n = 15 67.5 ± 8 (45–79)	p < 0.005	n = 45 59 ± 11 (29–79)
Cefamandole patients	n = 14 67.5 ± 9 (45–79)	p < 0.01	n = 30 59 ± 12 (29–79)
Vancomycin patients	n = 1 67		n = 15 62 ± 8 (45–79)

When WDI_{INT} is plotted against PT_{BL} for the cefamandole group there is a linear correlation of r = 0.8, p < 0.001 (Fig. 4). A similar plot for the vancomycin group revealed a poor, nonsignificant correlation r = 0.33, p > 0.05.

Some of the more important parameters were assessed and not found to be significantly different between GrI_{HR} and $GrII_{NR}$ (p > 0.05). Examples of the parameters without major differences are: (1) sex; (2) admission PT; (3) 2 hours postoperative PT; (4) NPO days postoperative; (5) initial warfarin dose mg/kg; (6) number of days before warfarin was started after surgery; (7) number of days vancomycin or cefamandole was given after surgery; (8) length of time on cardiopulmonary bypass pump; (9) length of surgery; (10) time of anesthesia; (11) total blood loss during surgery; (12) total blood lost after surgery; (13) total albumin given during surgery; and (14) total fresh frozen plasma given during and after surgery.

Discussion

The warfarin response in patients is extremely variable with the initial warfarin dose, interacting drugs, age, liver disease, and dietary vitamin K intake all described as influencing the prothrombin response to warfarin.[8,9]

The phenomenon observed might have been a normal variation, but a review of the literature revealed nothing which would indicate what the typical response should be to a total 15–20 mg of warfarin given over 2 days in the postoperative cardiac valve patient. In the study by O'Reilly and Aggler of 15 normal subjects, a 10 or 15 mg/day dose of warfarin produced a therapeutic PT in the range of 20 seconds in 5 and 3 days respectively.[10]

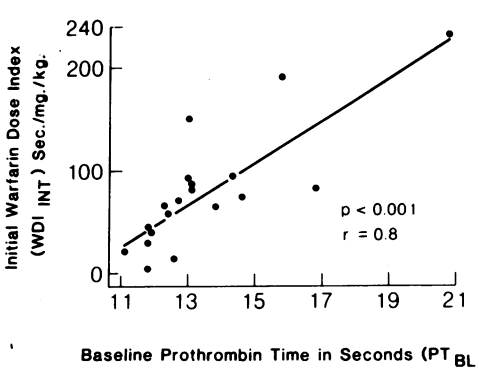

FIG. 4. Relationship between the baseline prothrombin time (PT_{BL}) and the initial warfarin dose index (WDI_{INT}) for cefamandole patients.

Hypoprothrombinemia resulting from the administration of a broad spectrum antibiotic has occurred in critically ill patients who were malnourished and treated with systemic antibiotics for a minimum of 7–10 days without vitamin K replacement.[11]

Cefamandole has been observed to cause hypoprothrombinemia at a faster rate than the previously reported antibiotics. But again these reports have been of very ill patients with poor oral intake and serious multisystem disease.[4,5]

Our data suggest that cefamandole may produce a significant hypoprothrombinemia and an enhanced response to warfarin in patients who were relatively well, adequately nourished before surgery with normal preoperative PTs, and NPO for only 24–96 hours after surgery.

The mechanism for this rapid cefamandole-induced hypoprothrombinemia is unknown. Cefamandole is highly secreted in bile and could lead to decreased vitamin K producing intestinal bacteria; however, there is no convincing evidence to show that vitamin K synthesized by such bacteria is available in any significant amounts for absorption, in man.[12] A direct effect of cefamandole on the synthesis of clotting factors at the hepatocyte level has been a subject of some interest but has not been documented *in vivo*.[13] Cefamandole contains the methylthiotetrazole side chain. This side chain has in part been implicated as a possible cause of hypoprothrombinemic bleeding diathesis in cefaperazone and in some clinical trials with moxolactam.[14]

Nagishima et al. have reported that older patients, with the same total plasma warfarin levels as younger patients, had a greater suppression of their vitamin K dependent clotting factors.[15] Pharmacodynamic factors such as a greater receptor sensitivity of the target organ to warfarin have been proposed as a possible mechanism for increased age-related sensitivity to the drug.[16,17]

The observed hypoprothrombinemic response could not entirely be attributed to age in our patients since the vancomycin patients who were of similar age as the GrI_{HR} cefamandole patients did not show the same hyper-response to warfarin. Age, however, may have played a role in the higher sensitivity to warfarin at discharge in the older GrI_{HR} patients.

Liver disease may reduce the synthesis of vitamin K-dependent clotting factors, thereby potentiating the action of warfarin.[18] Primary liver malfunction was not evident in any of our patients. Prior to surgery, their total protein,

albumin, total bilirubin, PT, serum alkaline phosphatase, and SGOT levels were all within normal limits.

Kingsley reported hepatic damage following profound hypothermia and cardiopulmonary bypass surgery. The damage was confirmed by autopsy, but only occurred in patients over 50 years old who had uncontrolled heart failure at the time of operation. The most notable finding in that study was the consistent elevation of alkaline phosphatase beginning at 2 weeks after surgery.[19] However, brief transient change in liver function following surgery could have occurred in our patients, thereby influencing the initial response to warfarin. This unlikely possibility cannot be ruled out since routine postoperative liver function tests are not done on our patients.

The impact on warfarin kinetics of bypass surgery, hypothermia, possible transient liver dysfunction, or cefamandole administration could not be assessed from the data.

Finally, the patients' pre- and post-operative dietary intake of vitamin K is important to the warfarin anticoagulation response. The minimum daily requirement of vitamin K in the adult human is estimated to be between 0.03 mcg/kg and 1.5 mcg/kg of body weight.[20] One patient in the study, upon being given a nutritional supplement containing 4.8 mcg/kg of vitamin K, before surgery developed a high resistance to warfarin.

The first sign of a vitamin K deficiency state is a prolongation of the PT. None of these patients had prolonged PTs on admission to surgery. GrI_{HR} patients who were older could have had marginal stores of vitamin K which may have been depleted as a result of surgical stress followed by their NPO state. However, neither surgical parameters (including the 2-hour postoperative PT, nor days NPO after surgery) were found to be significantly different between GrI_{HR} and $GrII_{NR}$ patients.

Conclusion

Compared to vancomycin, cefamandole may produce a significant postoperative hypoprothrombinemia in prosthetic cardiac valve replacement patients with apparently adequate nutrition and normal PTs before surgery. Warfarin's anticoagulant action is enhanced by the administration of cefamandole in the postoperative phase, and can lead to excessively high prothrombin times (>32 seconds) within 2 days of an initial warfarin dose. Older cardiac valve replacement patients are at a high risk for profound cefamandole-induced warfarin sensitivity early in the postoperative period of anticoagulant therapy. We recommend that prosthetic cardiac valve replacement candidates over 60 years old who have a baseline PT of 14 seconds or greater be started on no more than 5 mg per day of warfarin. A prospective study is underway to confirm this apparent pronounced sensitivity to warfarin's anticoagulant action by cefamandole, and to determine whether this effect is also true of the other cephalosporins being used as prophylaxis in the cardiac valve replacement surgical patient. The role of cephalosporins at the site of synthesis of the vitamin K-dependent clotting factors is not entirely clear and also needs further investigation.

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