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Retrospective Study of the Toxicity of Preparations of Vancomycin from 1974 to 1981

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A retrospective chart review of 98 patients treated with 100 courses of intravenous vancomycin was undertaken to better define its toxicity. Most of the patients carried diagnoses of *Staphylococcus aureus* or *Staphylococcus epidermidis* infection. Auditory toxicity was not seen, and fever and rash occurred in only 1 to 3% of the subjects. Phlebitis was noted in 13% of the cases and required discontinuation of therapy in 2%. Therapy was complicated by neutropenia (polymorphonuclear leukocyte count, ≤1,000 cells per cm^3) in 2% of the patients but was rapidly reversible. Nephrotoxicity was uncommon (5%) and reversible in subjects receiving vancomycin alone, even when the therapy was continued. However, 35% of the patients receiving vancomycin with an aminoglycoside developed significant elevations in serum creatinine. Although this high incidence may have been due to the patient population selected or to the aminoglycoside therapy alone, the possibility of additive toxicity between vancomycin and the aminoglycosides should be considered.

Vancomycin has been commercially available in the United States for over 20 years. It has strong bactericidal activity against many gram-positive bacteria, particularly the staphylococci. In the 1960s and 1970s, its use declined as semisynthetic penicillins became available to treat penicillinase-producing staphylococci. In more recent years, the use of vancomycin has increased significantly. Some of the reasons for this are the growing problem of *Staphylococcus epidermidis* infections in patients with prosthetic devices (6) and the emergence of epidemic methicillin resistance among *Staphylococcus aureus* in many centers (4, 7). In addition, vancomycin remains a major alternative for the treatment of bacterial endocarditis in penicillin-allergic patients and in those patients with infections due to penicillin-resistant, gram-positive organisms (3).

It has been postulated that impurities present in earlier formulations of vancomycin (and removed in more recent formulations) were responsible for much of the toxicity reported in previous studies (14). In support of this concept is the recent work by Aronoff et al. demonstrating that even massive doses of vancomycin are not nephrotoxic in rats (1). No clinical studies specifically addressing the issue of vancomycin toxicity have been done. Therefore, we sought to review the charts of a large number of patients treated with a modern preparation of vancomycin to define its toxicity.

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MATERIALS AND METHODS

Patients. The charts of 98 patients receiving intravenous vancomycin at Massachusetts General Hospital, Boston, between 1974 and 1981 were reviewed. Ninety-three of the patients were identified from the log book of the antibiotic blood level laboratory. The remaining five patients were identified from data obtained during a survey on the prevalence of methicillin-resistant *S. aureus*. Ninety-one patients had their therapy monitored with at least one serum vancomycin level. An attempt was made to review consecutive charts, although not all charts could be located.

Definitions. The diagnoses of rash, phlebitis, and ototoxicity were based on the opinion of the responsible physician. Fever was defined as a rectal temperature of at least 38.33°C. Nephrotoxicity was defined as a rise of at least 0.5 mg/dl in serum creatinine above a base-line value obtained before the initiation of therapy. Neutropenia was defined as an absolute granulocyte count of <1,000 cells per cm^3.

Vancomycin levels. Serum vancomycin concentrations were determined by an agar diffusion bioassay described in detail previously (8).

RESULTS

A total of 100 courses of vancomycin therapy given to 98 patients were surveyed. In the two patients that received two courses of vancomycin, the interval between courses was more than 6 months.

TABLE 1. Diagnosis in patients receiving vancomycin therapy

Diagnosis	No. of patients
S. aureus infections	
History of penicillin allergy	25
History of penicillin-induced neutropenia	4
Methicillin-resistant organism	13
S. epidermidis endocarditis	10
S. epidermidis infection	19
Enterococcal infection	4
Other infection with penicillin allergy	16
Chronic renal failure	3
Others	6

The diagnoses of the patients are shown in Table 1. Infection due to *S. aureus* in penicillin-allergic patients was the most common indication. Methicillin-resistant *S. aureus* and *S. epidermidis* infections were also common diagnoses.

There were 68 males and 30 females studied. The patients were treated from 2 to 70 days (mean, 18 days) and ranged in age from 1 to 85 years (mean, 51 years).

The incidence of adverse reactions documented in patients included the following.

(i) Rash. Drug eruptions occurred in 3% of the patients receiving vancomycin. One patient developed a maculopapular rash on his chest and back after 4 weeks of vancomycin therapy. The rash promptly disappeared when the vancomycin was stopped. The other medications the patient received were digoxin, warfarin sodium, docusate sodium (Colace; Mead Johnson & Co.), and ferrous sulfate, none of which was discontinued. Two other patients developed rashes while receiving vancomycin along with phenytoin sodium (Dilantin; Parke-Davis), and rifampin, respectively. In both instances, the rash necessitated the discontinuation of therapy. It could not be determined which drug was responsible for the eruption.

(ii) Phlebitis. Phlebitis occurred in 13% of all patients and required discontinuation of the drug in two cases. The mean length of therapy of patients with phlebitis was 26 days, compared with a mean of 28 days for the entire group. The dilution of vancomycin was similar in patients that developed phlebitis and those that did not: 2 g mixed in 500 ml of 5% dextrose in water (six patients), 2 g mixed in 1,000 ml of 5% dextrose in water (six patients), and 2 g mixed in 250 ml of dextrose in water (one patient).

(iii) Fever. Sustained fever thought to be due to vancomycin therapy was not seen in any of the patients. One person developed transient fever associated with wheezing and chills after receiving the first dose, but the rate of infusion was not noted. The patient had received a 6-day course of vancomycin approximately 2 weeks before this incident and was not rechallenged after the above reaction. Another patient developed a fever while receiving both vancomycin and rifampin, both of which were discontinued, and the fever subsided.

(iv) Ototoxicity. No clinically apparent cases of auditory toxicity were noted. Five patients had serial audiograms, none of which demonstrated a change. One patient (1%) developed vertigo while on vancomycin which appeared to resolve after the therapy was stopped.

(v) Neutropenia. Two of the 100 courses of therapy studied were complicated by neutropenia (2% of patients) thought to be due to vancomycin. One patient with prosthetic valve endocarditis and cytomegalovirus infection was noted to have neutropenia (leukocyte count, 1,200; 4% polymorphonuclear leukocytes; 2% bands; 4% eosinophils; 62% lymphocytes) on day 25 of therapy. The leukocyte count and differential promptly returned to normal when vancomycin therapy was stopped, and the only other medications the patient had received were digoxin, flurazepam, diazepam, oxycodone, and aspirin. The second patient was a 66-year-old female with group G streptococcal endocarditis and a history of penicillin allergy. After receiving vancomycin for 30 days, her leukocyte count fell to 2,700 (31% polymorphonuclear leukocytes, 1% bands, 11% eosinophils, 40% lymphocytes). Vancomycin therapy was discontinued, and the leukocyte count of the patient promptly rose to 10,000 with 90% polymorphonuclear leukocytes, 6% bands, and 4% lymphocytes. Other medications included docusate sodium (Colace) and heparin.

(vi) Nephrotoxicity. The outline of the patient population studied for the development of nephrotoxicity was as follows. Of the 100 courses of therapy studied, 6 could not be evaluated for the development of nephrotoxicity. Four of these patients were in renal failure before the initiation of vancomycin therapy. One patient had septicemia after suffering massive burns and was also receiving amphotericin B and amikacin. The final patient died in the operating room after receiving only 3 days of therapy, during which time his serum creatinine rose from 1 to 1.3 mg/dl.

Of the 94 courses of therapy evaluated, 34 patients were receiving aminoglycosides in addition to vancomycin (gentamicin, 23 patients; tobramycin, 10 patients; amikacin, 1 patient). Of

TABLE 2. Patients with nephrotoxicity

Age (years)	Sex	Diagnosis[a]	Daily dose (g)	Length of prescription (days)	Change in serum creatinine (mg/dl)	Peak/trough levels (μg/ml)[b]	Other drugs
73	F	*S. aureus* sepsis	2.0	30	1.0 → 3.2	76/65	
59	M	*S. epidermidis* PVE	2.0	70	1.3 → 2.3	/39	
65	M	*S. pyogenes* cellulitis	1.0	26	1.2 → 1.7	35/30	Gentamicin
60	M	*S. aureus* sepsis	1.5	28	2.0 → 6.4	49/48	Furosemide-rifampin
54	M	Wound infection	2.0	7	1.1 → 3.4	25	Gentamicin
61	M	Prosthetic hip infection	1.5	30	1.0 → 2.0	19/12	Tobramycin
82	F	SBE	1.5	30	0.7 → 1.6	20/	Tobramycin-furosemide
61	M	SBE	2.0	26	1.1 → 2.8	36/21	Gentamicin
31	M	Burns, *S. epidermidis* sepsis		4	1.2 → 1.7		Gentamicin
74	F	Enterococcal PVE	2.7	13	2.1 → 4.0	37/124	Gentamicin
55	F	Osteomyelitis	1.5	17	1.0 → 1.5	30/19	Gentamicin
37	F	*S. epidermidis* PVE	2.0	26	0.8 → 2.6	26/	Gentamicin
52	F	*S. epidermidis* PVE	2.0	70	1.1 → 1.8	38/27	Gentamicin
22	M	*S. epidermidis* sepsis, VSD	2.0	28	1.3 → 2.2	22/	Gentamicin
85	F	*S. aureus* sepsis	1.5	30	1.5 → 2.1	30/27	Tobramycin

[a] PVE, Prosthetic valve endocarditis; SBE, subacute bacterial endocarditis; VSD, ventricular septal defect.
[b] Before rise in serum creatinine.

these 34 patients, 12 developed a significant increase in serum creatinine. Three of the remaining patients also developed an increase in serum creatinine. Therefore, the incidence of nephrotoxicity was 35 and 5% in patients receiving vancomycin with and without an aminoglycoside, respectively.

Specific details of the patients who developed nephrotoxicity are shown in Table 2. The mean age of the group was 58 years, higher than the mean age (51 years) of the patients who did not develop nephrotoxicity. This difference was not statistically significant ($P < 0.05$). The mean length of vancomycin therapy was significantly longer in this group (29 versus 20 days; $P \leq 0.05$). The three individuals that developed nephrotoxicity without concomitant aminoglycoside therapy all had high serum levels (trough, 30 to 65 μg/ml) before the rise in creatinine. In two of these individuals, the creatinine returned to its base-line value after dosage adjustment despite continuation of the drug. Of the 12 individuals that developed nephrotoxicity while receiving vancomycin and an aminoglycoside, 5 had one of the antibiotics discontinued because of the rise in creatinine.

DISCUSSION

Early reports suggested that vancomycin is frequently associated with toxicity. In 1962, Geraci et al. reported a 5% incidence of rash and drug fever in a group of 85 treated patients (5). In addition, Woodley and Hall reported that almost 30% of the patients studied developed phlebitis (14). Ototoxicity, which may be transient or permanent, seems to be closely related to excessively high serum levels (14). The exact incidence of nephrotoxicity secondary to vancomycin is difficult to document, even in earlier studies. In the series of Geraci and Hall, no definite cases of nephrotoxicity were reported, although 5 of 19 patients developed elevated blood urea nitrogen concentrations, an effect thought to be related to congestive heart failure (5). Of the 54 patients treated by Waisbren et al., 3 developed nephrotoxicity which seemed to be related to the vancomycin therapy (10).

In the present series, the incidence of vancomycin-induced rash and fever was low. Phlebitis occurred in 13% of the patients, an incidence which appears to be less frequent than those of earlier reports (14). Ototoxicity was not seen, an observation which may be a reflection of the fact that most patients had serum levels monitored. Only 1 patient of the 91 in whom serum levels were available for analysis had a level of >80 μg/ml. Nephrotoxicity was uncommon in patients receiving vancomycin alone (i.e., without an aminoglycoside). Only 3 of 60 patients in this category had an increase in serum creatinine, and 1 of these patients had a rapidly fatal underlying disease. The two other patients showed a prompt return of serum creatinine to normal levels when the dose and serum concentrations were adjusted. Of note is the high incidence of nephrotoxicity in patients receiving vancomycin with an aminoglycoside. Of these patients, 35% had significant rises in serum creatinine. There are several possible explanations for this high incidence of nephrotoxicity. Aminoglycoside

therapy alone is a well-recognized cause of nephrotoxicity; however, most series report a considerably lower incidence (10 to 26% [9, 11]). Another explanation is that the high incidence is an artifact of our method of identifying patients. Patients were identified from the records of the antibiotic blood level laboratory. This could introduce a bias in favor of the selection of either high- or low-risk patients. It is possible that the most seriously ill patients received both vancomycin and gentamicin and were more frequently monitored with serum levels than those with less serious underlying diseases. In addition, six of the patients receiving vancomycin with aminoglycosides carried a diagnosis of endocarditis which could have contributed to their renal insufficiency. It is also possible that our patients may have been followed more closely by their physicians, partially accounting for the low incidence of toxicity in those treated with vancomycin alone. Only a controlled study can answer these questions; however, the data raise the possibility that vancomycin and the aminoglycosides have additive nephrotoxicity. In support of this possibility is the recent report by Wold and Turnipseed demonstrating that the combination of tobramycin and vancomycin are synergistically nephrotoxic in rats (13).

Finally, two patients were identified whose therapy was complicated by reversible neutropenia. This has only recently been described as a side effect of vancomycin therapy (2, 12). This study suggests that it may be more common than the literature suggests; we are aware of at least three additional cases of vancomycin-induced neutropenia occurring in our hospital but not included in this series. Therefore, patients should be monitored frequently for blood counts while receiving vancomycin.

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