ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1982, p. 592–594
0066-4804/82/040592-03$02.00/0

Vol. 21, No. 4

Minimal Nephrotoxicity with Cephalosporin-Aminoglycoside Combinations in Patients with Neoplastic Disease

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Received 13 October 1981/Accepted 7 January 1982

Patients with cancer and suspected sepsis were treated in a prospective, randomized trial with one of four cephalosporin-aminoglycoside combinations: cephalothin and tobramycin; cephalothin and gentamicin; cefamandole and tobramycin; or cefamandole and gentamicin. Carbenicillin was added if the absolute granulocyte count was <1,000/mm^3. Of 199 patients receiving 20 or more doses of an aminoglycoside and having serial determination of serum creatinines, nephrotoxicity developed in seven (3.5%) given any of the four combinations. There were no significant differences between patients receiving either cephalosporin or either aminoglycoside. Nephrotoxicity developed less frequently among children (2 of 125; 1.6%) than adults (5 of 74; 6.8%).

Combinations including an aminoglycoside with a cephalosporin or an antipseudomonal penicillin or both are often used for empiric treatment of infections in patients with neoplastic diseases (1, 3–5). Although the potential nephrotoxicity of the aminoglycosides used in such combinations has been of continuing concern (2, 7), actual liabilities have not been well delineated. To assist in defining such liabilities, we undertook a prospective, randomized trial to determine the incidence of nephrotoxicity in patients with neoplastic disease at the Memorial Sloan-Kettering Cancer Center.

(This study was presented in part at the First International Symposium on Infections in the Immunocompromised Host, 1–5 June 1980, Veldhoven, The Netherlands.)

MATERIALS AND METHODS

Patients were randomly assigned to receive one of four cephalosporin-aminoglycoside combinations: cephalothin and tobramycin, cephalothin and gentamicin, cefamandole and tobramycin, or cefamandole and gentamicin. Doses of the cephalosporins were 200 mg/kg per day intravenously in divided doses every 4 h. Aminoglycoside doses were a 2-mg/kg initial loading dose intravenously followed by 5 mg/kg per day in divided doses every 6 h. If the absolute granulocyte count was <1,000/mm^3, carbenicillin (500 mg/kg per day intravenously) in divided doses every 4 h was added.

A base-line serum creatinine had to be ≤2.0 mg/dl in order for a patient to be eligible for randomization. Serum creatinine levels were determined at base line, on day 3, on the last day of combination therapy, and within 72 h of stopping therapy. Patients had to receive at least 5 days or 20 doses of an aminoglycoside, whichever was greater, to be evaluable. Aminoglycoside levels were determined by radioimmunoassay within 72 h of starting therapy, and aminoglycoside doses were adjusted to maintain the 30-min peak serum concentrations between 5 and 10 μg/ml and trough concentrations at <2 μg/ml. Nephrotoxicity was defined as a rise in serum creatinine of >0.4 mg/dl above the base-line serum creatinine level at any time during or after combination antibiotic therapy.

Patients receiving other potentially nephrotoxic agents, such as cisplatinum or amphotericin B, were excluded from evaluation of nephrotoxicity when these agents were given concomitantly or within 72 h before the rise in serum creatinine. Similarly, patients presenting with septic shock were eliminated from evaluation of nephrotoxicity. The Fisher exact test was used to test for differences between proportions.

RESULTS

Of the 241 patients entered in the study, 199 were evaluated for nephrotoxicity. Of the 42 patients excluded from the analysis of nephrotoxicity, 28 received less than 5 days of combination therapy or did not have sufficient serial serum creatinine determinations done. Seven patients received amphotericin B; three patients had septic shock; two patients received cisplatinum; and one patient each had myeloma kidney and a renal abscess. All 14 of these patients developed nephrotoxicity. Their distribution among the four antibiotic treatment groups were: six cephalothin and tobramycin, one cephalothin and gentamicin, four cefamandole and tobramycin, and three cefamandole and gentamicin.

The study group was compartmentalized by age as children (1 through 17 years; mean, 9.4 years) and adults (18 to 68 years; mean, 36 years). The age distributions were similar in each antibiotic treatment group. There were 122 males and 77 females.

Of the 125 children, 62 had leukemia, 10 had lymphoma, and 53 had solid tumors. Of the 74

TABLE 1. Nephrotoxicity

Drug treatment	No. showing nephrotoxicity		
	Adults	Children	All patients
Cephalothin with:			
Tobramycin	1/14	0/26	1/40
Gentamicin	2/16	1/31	3/47
Total	3/30 (10)[a]	1/57 (1.8)	4/87 (4.6)
Cefamandole with:			
Tobramycin	1/19	0/37	1/56
Gentamicin	1/25	1/31	2/56
Total	2/44 (4.5)	1/68 (1.5)	3/112 (2.7)
Gentamicin with:			
Cephalothin	2/16	1/31	3/47
Cefamandole	1/25	1/31	2/56
Total	3/41 (7.3)	2/62 (3.2)	5/103 (4.9)
Tobramycin with:			
Cephalothin	1/14	0/26	1/40
Cefamandole	1/19	0/37	1/56
Total	2/33 (6.1)	0/63 (0)	2/96 (2.1)
Overall total	5/74 (6.8)	2/125 (1.6)	7/199 (3.5)

[a] Numbers in parentheses are percentages.

adults, 34 had leukemia, 9 had lymphoma, and 31 had solid tumors. These three disease categories were equally distributed among the four antibiotic groups.

Of 199 patients, 168 (84.4%) were neutropenic (absolute granulocyte count of $<1,000/mm^3$) at time of random assignment to an antibiotic combination. The distribution of neutropenic patients (and carbenicillin usage) was equal among the four antibiotic treatment groups.

The mean duration of combination antibiotic therapy was 11.2 days in the adult group and 11.0 days in the children's group. The duration of therapy did not vary significantly from one treatment group to another.

Nephrotoxicity: Nephrotoxicity developed in seven of 199 (3.5%) patients evaluated (Table 1). Four of 87 (4.6%) patients receiving cephalothin and an aminoglycoside developed nephrotoxicity, compared with three of 112 (2.7%) patients receiving cefamandole and aminoglycoside. There were no significant differences between these groups.

Of patients receiving gentamicin and a cephalosporin, 4.9% (5 of 103) developed nephrotoxicity, compared with 2.1% (2 of 96) receiving tobramycin and a cephalosporin. Again, there were no significant differences between these groups.

Of children who were evaluated, only 2 of 125 (1.6%) developed nephrotoxicity. There were no differences among all groups.

Among the 74 adult patients who were evaluated, 5 (6.8%) had nephrotoxicity. Of the 14 patients who received cephalothin and tobramycin, 1 (7.1%) developed nephrotoxicity, and of the 16 patients who received cephalothin and gentamicin, 2 (12.5%) developed nephrotoxicity, for a total of 3 of 30 (10.0%) who received cephalothin plus either aminoglycoside.

In the cefamandole plus either aminoglycoside group, 2 of 44 (4.5%) patients developed nephrotoxicity. Although there was a higher percentage of nephrotoxicity, 10% versus 4.5%, in patients who received cephalothin and aminoglycoside compared with patients who received cefamandole and aminoglycoside, these differences were not significant. No significant differences were noted between groups receiving gentamicin or tobramycin.

DISCUSSION

Nephrotoxicity with cephalosporin and aminoglycoside combinations occurred more often in adults (6.8%) than in children (1.6%). Nephrotoxicity occurred in only 3.5% of all patients evaluated in this study.

Table 2 presents differences among the current study and those previously reported (2, 7). Patients in the current study were younger and had normal renal function at the time of randomization; received a longer course of aminoglycoside therapy as a prerequisite for evaluation; received a loading dose of 2 mg of aminoglycoside per kg followed by 6-hourly doses of aminoglycoside; had peak serum aminoglycoside concentrations determined at 30 min after an intravenous dose was completed; and had trough serum aminoglycoside concentrations of <2 μg/ml. Also, more than 84% of patients received carbenicillin in addition to the cephalosporin-aminoglycoside regimen.

Nephrotoxicity with cephalothin and aminoglycoside antibiotic combinations occurred in 10% of adult patients compared with 25.5% reported by Wade et al. (7). Furthermore, our 6.8% incidence of nephrotoxicity with gentamicin or tobramycin in combination with a cephalosporin in adults is lower than the 19.2% incidence of nephrotoxicity with either gentamicin or tobramycin in combination with antibiotics other than cephalosporins in another study (6).

To make comparisons between the current study and the EORTC study (2), nephrotoxicity must be redefined in accordance with that study's definition. Unlike Wade et al. (7) and the current study, the EORTC definition of nephrotoxicity was less restricted. Table 3 compares our results with those of the EORTC and demonstrates a similar incidence of intermediate renal dysfunction, but a reduced incidence of severe renal dysfunction among patients receiving cephalothin and an aminoglycoside.

Knowing fully that patients in our study may be younger than those in previous studies, and that our patients' base-line renal function was, indeed normal, we conclude that although neph-

TABLE 2. Comparison of studies reporting on the incidence of nephrotoxicity among patients receiving cephalothin-aminoglycoside combinations

Study	Determination									
	Mean Age (yr)	Renal function	Minimum no. of Aminoglycoside doses	Loading dose of aminoglycoside	Dose schedule of aminoglycoside	Aminoglycoside concn determined	Time peak aminoglycoside concn obtained after dose (min)	Trough aminoglycoside concn of <2 μg/ml	Received carbenicillin	% of adults with nephrotoxicity
This report	36	Normal	20	yes	Every 6 h	yes	30	yes	yes	10 (3/30)
Wade et al. (7)	60	Not stated	9	yes	Every 8 h	yes	60	Not stated	no	25.5 (12/47)
EORTC (2)	43	Normal and abnormal	Not stated	no	Every 6 h	Not available	Not stated	Not stated	no	see Table 3

TABLE 3. Analysis of renal dysfunction among cancer patients receiving cephalothin-aminoglycoside combinations using the EORTC definition of renal dysfunction (2)

Study	% of patients with renal dysfunction[a]	
	Intermediate	Severe
This report	6.7 (2/30)	3.3 (1/30)
EORTC	4.4 (6/135)	11.9 (16/135)

[a] Intermediate defined as serum creatinine of <1.5 to 2.5 mg/dl. Severe defined as serum creatinine of <1.5 to >2.5 mg/dl.

rotoxicity is more frequently observed in adults than in children, cephalosporin-aminoglycoside antibiotic combinations, as used in our patient population, do not result in as high an incidence of nephrotoxicity as reported in previous studies (2, 7). Caution needs to be taken in patients with neoplastic diseases who are neutropenic and febrile and require broad-spectrum antibiotic coverage. That caution should be in the form of closely monitoring aminoglycoside serum concentrations and parameters of renal dysfunction. If these precautions are properly taken, we believe such patients can be treated safely and effectively with these cephalosporin-aminoglycoside combinations.

ACKNOWLEDGMENTS

We gratefully acknowledge the assistance given by the Division of Pharmacy of Memorial Sloan-Kettering Cancer Center.

This research was supported by a grant from Eli Lilly & Co., Indianapolis, Ind.

LITERATURE CITED

1. **Armstrong, D.** 1980. Infections in patients with neoplastic diseases, p. 129–158. *In* J. Verhoef, P. K. Peterson, and P. G. Quie (ed.), Infections in the immunocompromised host—Pathogenesis, prevention and therapy. Elsevier/North Holland Biomedical Press, Amsterdam.
2. **EORTC International Antimicrobial Therapy Project Group.** 1978. Three antibiotic regimens in the treatment of febrile granulocytopenic patients with cancer. J. Infect. Dis. **137**:14–29.
3. **Klastersky, J.** 1980. Therapy of bacterial infections in cancer patients, p. 207–229. *In* J. Verhoef, P. K. Peterson, and P. G. Quie (ed.), Infections in the immunocompromised host—Pathogenesis, prevention and therapy. Elsevier/North Holland Biomedical Press, Amsterdam.
4. **Love, L. L., S. C. Schimpff, C. A. Schiffer, and P. H. Wiernik.** 1980. Improved prognosis for granulocytopenic patients with gram-negative bacteremia. Am. J. Med. **68**:643–648.
5. **Singer, C. F., M. H. Kaplan, and D. Armstrong.** 1977. Bacteremia and fungemia complicating neoplastic disease: a study of 364 cases. Am. J. Med. **62**:731–742.
6. **Smith, C. R., J. J. Lipsky, O. L. Laskin, D. B. Hellmann, E. D. Mellits, J. Longstreth, and P. S. Lietman.** 1980. Double-blind comparison of the nephrotoxicity and auditory toxicity of gentamicin and tobramycin. N. Engl. J. Med. **302**:1106–1109.
7. **Wade, J. C., B. G. Petty, G. Conrad, C. R. Smith, J. J. Lipsky, J. Ellner, and P. S. Lietman.** 1978. Cephalothin plus an aminoglycoside is more nephrotoxic than methicillin plus an aminoglycoside. Lancet **ii**:604–608.