Clinical Experience with Cefazolin in Large Doses Combined with Aminoglycoside in Blood Disease

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INTRODUTION

The parenteral administration of cephalosporin has been widely used for the treatment of infections due to gram-negative bacilli.[1] Patients with malignant blood diseases very frequently suffer from marked neutropenia and/or immunological defect as a result of intensive chemotherapy and blood disease itself.[2] Severe infection with neutropenia is the most serious problem in the treatment of malignant blood disease. A large dose of cephalosporin to reach effective serum level for severe infection has been adopted. Although the bactericidal effect of cephalothin (CET) is less than that of cephaloridine (CER),[3] CET has been preferably used in these patient because of the greater nephrotoxicity of CER. Furthermore, the combination of CET plus gentamicin (GM) or kanamycin (KM) has been tried for infection in patients with malignant blood diseases. The combination of CET and GM was implicated in acute tubular necrosis.[4] Recently, a new cephalosporin, cefazolin (CEZ), was introduced.[5] CEZ was reported as having the same bactericidal effect on gram-negative bacilli as CER[5] while also having less nephrotoxicity than CER.[6]

Until now, reports on CEZ given in large doses to patients with blood diseases were rarely found. Hence, this study was undertaken to observe clinically the efficacy and side effects of CEZ in large doses combined with aminoglycoside in patients with blood deseases.

PATIENTS AND METHODS

The patients in this study included of 11 males and 9 females between 17 and 72 year-old who were hospitalized to the Third Department of Internal Medicine Yamaguchi Universisy School of Medicine from Feb., 1973 to March, 1975. The blood diseases of these patients were leukemia,

aplastic anemia, malignant lymphoma. The therapies for blood diseases were as follws; The combination of daunorubicin, cytosine arabinoside and prednisolone (DAP)[7] or cyclophosphamide, vincristine, cytosine arabinoside and prednisolone (COAP)[8] were prescribed for acute leukemia and blastic crisis of chronic granulocytic leukemia, Nitromin®, vincristine, procarbazine, prednisolone and bleomycin (NOPP-Bleo) for Hodgkin's disease (Table 1), cyclophosphamide, vincristine, prednisolone (COP)[9] and bleomycin (COP-Bleo)for non-Hodgkin's lymphoma, and oxymetholone (1.5–3.0 mg/kg/day) or methenolone (2mg/kg/day) for aplastic anemia.

Table 1. NOPP-Bleomycin Combination Therapy

Drugs	Dose	Course																	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17…28	29
Nitromin	100mg.	X							X										X
Vincristine (Oncovin®)	2mg.	X							X										X
Procarbazine	100mg./M²	50	100	X	X	X	X	X	X	X	X								50
Prednisolone	40mg./M²	X	X	X	X	X	X	X	X	X	X	40	20	10					X
Bleomycin	15mg.				X				X				X				X		

The combination therapy was repeated every 28 days. Bleomycin never exceeded the total dose of 300mg.

On febrile episode over 38.5°C, antibiotics therapy was initiated soon after obtaining the samples for bacteriological examination from blood, urine, pharyngeal mucus, sputum and pus. Complete blood count, serum glutamic pyruvic transaminase (SGPT), blood urea nitrogen (BUN),alkaline phosphatase, serum creatinine, Coombs test, bilirubin and urinalysis were examined prior to, during and after antibiotics therapy. Sensitivity of bacteria to antibiotics was determined by the disc technique (The discs were purchased from Eiken Kagaku Co., Tokyo, Japan). The results of the disc technique were classified into four categories; (−), (+), (++), and (+++), with (−) and (+) representing no sensitivity and (+++) representing the greatest sensitivity.

In this study, all of the antibiotics were given by intravenous route but KM was injected intramuscularly in patients without thromocytopenia. Initially chemotherapy with CEZ was given, followed by aminoglycoside three days after the beginning of CEZ in the cases in which there was no subsidence of fever with only CEZ. For aminoglycosides, KM was preferred when the causative organism was sensitive to both KM and GM. In cases where Pseudomonas were detected, carbenicillin (CBPC) or sulbenicillin (SBPC) was added to CEZ and GM.

The standard dosage of CEZ in patients with neutropenia was 8–12g., daily. A dose of CEZ 2–3g. in 100ml physiological saline or 5% glucose was infused every 6 hrs. over a period of 1 to 2 hrs. Four hundred to five hundred mg of KM was given in 100ml physiological saline, every 12hrs. over a period of 1 to 2hrs. A dose of GM 30–40mg. in 20ml. physiological

Table 2. Cases treated with cefazolin

Case No.	Sex. Age	Blood disease	Probable initial pathogen(s)	Sourse of positive culture	Combined use of antibiotics	Response to therapy
1	F. 22	AGL	Pseudo, Klebsiella, Serratia	Pharyngeal mucus	none	success
2	M. 71	AMoL	not detected	—	GM	failure
3	F. 48	AMoL	Pseudo, Cloaca, Enterococcus	Pharyngeal mucus	GM. CB-PC	success
4	F. 72	AMoL	Pseudo, Cloaca, Enterococcus	sputum	GM	failure
5	M. 56	AMoL	not detected	—	GM	success
6	M. 31	AMoL	Entero, Cloaca, Klebsiella	Pharyngeal mucus	GM	failure
7	M. 50	AMoL	not detected	—	GM	failure
8	F. 25	APGL	Pseudomonas	Pharyngeal mucus	GM or KM	failure
9	M. 69	AGL	Klebsiella	sputum	KM	failure
10	M. 48	Blastic crisis of CGL	Klebsiella	sputum	GM	success
11	M. 43	Blastic crisis of CGL	Pseudomonas	pus	GM or KM	failure
12	F. 49	Erythroleukemia	Klebsiella	blood	KM	success
13	M. 57	Erythroleukemia	E. coli, Enterococcus	Pharyngeal mucus	GM	success
14	M. 52	Erythroleukemia	Klebsiella, E. coli, Pseudo	sputum	KM, SB-PC	failure
15	M. 14	Malignant lymphoma	not detected	—	none	success
16	M. 34	Malignant lymphoma	not detected	—	none	success
17	M. 50	Hodgkin's disease	Klebsiella	sputum	KM	success
18	M. 23	Aplastic anemia	Klebsiella	Pharyngeal mucus	KM	failure
19	M. 17	Aplastic anemia	Klebsiella, Morganella	Pharyngeal mucus	GM or KM	failure
20	F. 52	Aplastic anemia	Staphylococcus aureus	Pharyngeal mucus	none	success

AGL: acute granulocytic leukemia
AMoL: acute monocytic leukemia
APGL: acute progranulocytic leukemia
CGL: chronic granulocytic leukemia
Pseudo: Pseudomonas
Cloaca: Enterobacter cloacae
Entero: Enterococcus
E. coli: Escherichia coli
GM: gentamicin
CB-PC: carbenicillin
SB-PC: sulbenicillin
KM: kanamycin

saline was given within one minute, every 6–8hrs. Twenty to thirty grams of CBPC or SBPC were given in 1,000ml. physiological saline was infused continuously for a period lasting 24hrs. through a different route from that of GM.

Absence of fever for 7days after stopping antibiotic(s) was regarded as a sign of therapeutic success, unless steroid had not been given for these seven days. When there was no clinical and bacteriological response to one regimen of antibiotic (s) within three days, the regimen was regarded as a therapeutic failure.

RESULTS AND DISCUSSION

The cases treated with cefazolin are summarized in Table 2. Therapeutic success was achieved in ten of twenty patients (50%). Five of the ten patients who suffered from severe infection due to gram-negative bacilli were cured with a combination of CEZ and aminoglycoside. Two patients (Case 15 and 16) with infection of which the causative organism was not detected were also cured by CEZ alone. There have been many reports about various combinations among CET, CBPC, GM and KM. Fifty percent therapeutic success rate in our study was less than the 82% with CET, CBPC and GM achieved in another study[10] or the 60% with CBPC and CET in neutropenic patients of one other study.[11] Our results were comparable to the success rate of 52% with CBPC and GM in cancer patient with neutropenia[12], the 53% rate with CBPC and KM[11] and the 53% rate with CBPC, CET, GM, methicillin and clindamycin in patients with leukemia and neutropenia.[13] As far as we could review, empirical therapy with CET, CBPC and GM was most effective for infection in patients with malignant blood disease. But it was difficult to compare these figures because of the differences of the underlying diseases and supplementary therapies such as leukocyte transfusion. Leukocyte transfusion has been effective in the treatment of infection with acute leukemia [14], and the underlying disease was a major determinant of fatality in gram-negative bacteremia.[15]

Ten of twenty patients failed to respond or died. Six pntients (Case 2, 4, 6, 8, 9 and 11) were in terminal stage of leukemia. It was reported that antibiotic therapy was effective in leukemia patient who went into complete or partial remission.[16]

The relationship between the peripheral neutrophil count and therapeutic result is shown in Fig. 1. The cases in which peripheral neutrophil count recovered over 500/mm^3 after chemotherapy resulted in

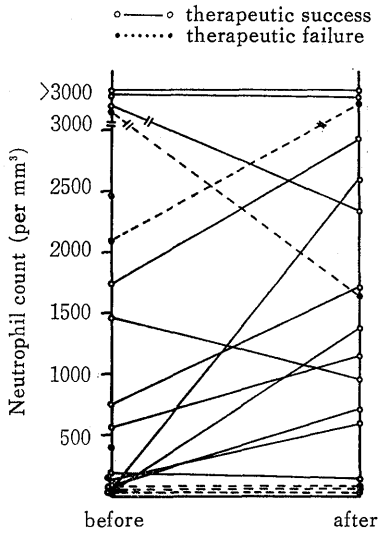

Fig. 1. Relationship between response of neutrophil count to infection and therapeutic result.
Only initial neutrophil count was pointed in black circle when the patient was died of bleeding during the treatment of infection.

therapeutic success with the exception of two patients (Case 2 and 14). The infection of Case 14 was improved by a combination of GM and lincomycin, although this case had never responded to combination of CEZ, KM and SBPC. Case 1 showed subsidence of fever and sore throat with CEZ when the peripheral neutrophil count increased up to 350/mm^3, in spite of the presence of orgnisms insensitive to CEZ. However, two aplastic anemia (Case 18 and 19) and one leukemia (Case 7) had neutrophil count less than 100/mm^3 and all of them failed to respond to treatment. Case 18 received a continuous administration of GM 80mg., daily. Case 19 died of infection and intracranial bleeding. The prognosis of infection was reported to depend on the neutrophil count[17] and its reserve against infection.[18] Most antibiotics were less effective in patients with neutropenia, although CBPC in large doses was reported to be effective regardless of neutropenia.[19] Although CEZ combined with GM was proved to be effective for infection in only Case 13 with neutropenia less than 200/mm^3, peripheral neutrophil count appeared to be a major factor to decide the prognosis of severe infection.

Antibiotic sensitivity to initial causative organism is shown in Table 3. Gram-negative bacilli were cultured by initial bacterilogical examination in fourteen patients and gram-positive bacilli in one patient and no pathologic bacteria in five patients. Three of nine Klebsiella strains were

Table 3. Antibiotic sensitivity to organism found in initial bacteriological examination

	KM		GM		total
	sensitive	insensitive	sensitive	insensitive	
Sensitive to CEZ					
Klebsiella	4	2	5	1	6
E. coli	2	0	2	0	2
Staphylococcus aureus	1	0	1	0	1
insensitive to CEZ					
Pseudomonas	—	—	6	0	6
Cloaca	2	1	3	0	3
Klebsiella	2	1	2	1	3
Morganella	0	1	1	0	1
not examined to CEZ					
Enterococcus	0	4	2	2	4
Serratia	0	1	1	0	1

insensitive to CEZ, and one of them was also insensitive to KM and GM. But they were cured with the combination of CEZ (or CET) and GM (or KM). In addition, clinical response was not observed by CET in large doses, at most 18g., daily for sepsis due to Klebsiella in an elderly woman with neutrophil count more than 3,000mm^3, although the causative organism was sensitive to cephalosporin. She responded well to the combination of CET (or CEZ) and KM. KM and CET were reported to be synergistic in vitro for many Klebsiella isolates.[20] These suggest that it is of value to use KM before cephalosporin is increased in dosage for infection due to cephalosporin-sensitive Klebsiella, although with regard to the sensitivity in vitro of antibiotics to Klebsiella, it was reported that KM and CET were less effective.[21] On the other hand, CEZ had more activity against Klebsiella in vitro study than CET.[22] KM may be more effective against Klebsiella combined with CEZ than CET, although the synergistic or additive effect between CEZ and KM remains unclear. Mixed infection with Pseudomonas, Enterococcus, Enterobacter cloacae, Morganella and/or Serratia was usually observed in the initial bacteriological examination, as shown in Table 2. These were all insensitive to CEZ, and most of them were sensitive to KM and/or GM, as shown in Table 3. Therefore, it can be said that CEZ should be given combined with aminoglycoside in patients with blood diseases.

Clinical evidence of CEZ efficacy has already been reported.[23),24)] Most of the patients in these reports were effectively treated by CEZ 2–4g., daily for infections due to gram-negative bacilli but their underlying

diseases and peripheral neutrophil counts were not described in detail. The fever of Case 17 responded to CEZ 12g. daily combined with KM 1g. daily but not with CEZ 4g. daily. In addition, the fever of one patient with carcinoma subsided with CEZ 8g. daily but not with 4g. daily, in our clinical experience. CEZ 8–12g. daily was necessary in these two patients with underlying diseases as the usual dose of CEZ was not effective.

The influence of total dose of CEZ to SGPT level is shown in Fig. 2. Twelve of twenty patients showed SGPT elevation, in various degree depending on the case, after antibiotics therapy, while the other showed a rather decreased SGPT level from the initial level. The antibiotics therapy did not seem to influence SGPT level significantly and a correlation did not appear between the total dose of CEZ and the SGPT elevation. Only one patient (Case 19) showed a marked elevation of SGPT level from 134u. to 1509u. This patient had been receiving blood transfusion, platelet rich plasma and hepatotoxic drugs, such as oxymetholone for several months prior to this GPT elevation.

The influence of total dose of CEZ to BUN level is shown in Fig. 3. Seven of nineteen patients showed BUN elevation, although the elevation was not so severe that CEZ or other antibiotic(s) should be discontinued. Six of the seven patients also received GM or KM, as well as CEZ. There

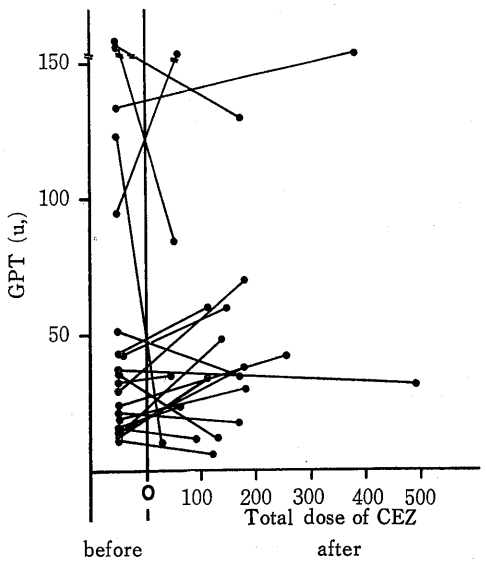

Fig. 2. Influence of total dose of CEZ to SGPT level.
SGPT levels during CEZ therapy were used in case 2, 5, 6, 9, 17and 19 as SGPT levels after therapy were not availabe in these patients.

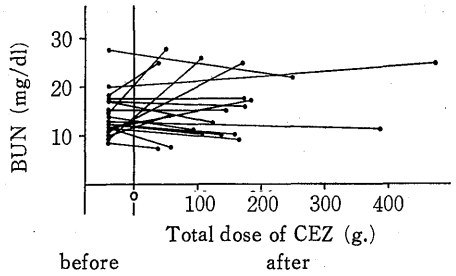

Fig. 3. Influence of total dose of CEZ to BUN level.

were no cases who developed oliguria or anuria and showed abnormal urinalysis, except for an increased excretion of granular casts in at least two cases.

None of the patients had phlebitis along blood vessels during infusion of CEZ in large doses. Only one patient developed generalized exanthemas associated with CEZ administration. The exanthemas disappeared soon after stopping the CEZ. A large dose of CEZ (12g. daily) in small series was reported to be tolerated well by patients showing no evidence of hematoxicity, hepatotoxicity or nephrotoxicity.[22] Although it is often difficult to determine the cause of the toxicity because of the combined use of antibiotics and other drug(s), it seemed that the combination of CEZ in large doses and aminoglycoside could be used without significant side effects.

In conclusion, aminoglycoside should be added to the initial therapy with CEZ in large doses and the combination can be used effectively for severe infection due to gram-negative bacilli in patients with blood diseases. This combination did not cause significant side effect except for generalized exanthema when administered intravenously.

SUMMARY

The clinical efficacy of cefazolin (8–12g. daily) combined with aminoglycoside for severe infection was evaluated in 20 patients with blood diseases. In ten of twenty patients, therapeutic success was achieved. Three patients with infection of which the causative organism was not detected responded to cefazolin alone or with gentamicin. But the usual dose of cefazolin (2–4g. daily) was not effective against infections due to gram-negative bacilli in a patient with Hodgkin's disease although there were sufficient neutrophil count. As mixed infection with organisms which were insensitive to cefazolin were frequently observed in patients with

neutropenia or malignant blood diseases and most of cefazolin-insensitive organisms were sensitive to aminoglycoside, aminoglycoside should be included in the initial therapy of CEZ in large doses for severe infection due to gram-negative bacilli in these patients. There were no significant side effects except for one case of generalized exanthemas associated with cefazolin in large dose combined with aminoglycoside.

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