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Ofloxacin versus Co-Trimoxazole for Prevention of Infection in Neutropenic Patients following Cytotoxic Chemotherapy

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The efficacy of ofloxacin in preventing infection in neutropenic patients following cytotoxic chemotherapy was evaluated and was compared with that of co-trimoxazole. A total of 102 patients with hematological malignancies were randomly selected to receive either co-trimoxazole or ofloxacin. All patients were monitored for compliance, occurrence of infection, and drug-related side effects. A surveillance culture of a rectal swab was performed regularly. A total of 25 of the 52 patients (48%) who received co-trimoxazole and 11 of the 50 patients (22%) who received ofloxacin developed fever during the study period ($P < 0.025$). Gram-negative bacteremia occurred in nine patients in the co-trimoxazole group (17%) but in only one patient (2%) in the ofloxacin group ($P < 0.05$). No patient in either group had documented gram-positive bacterial or *Pneumocystis carinii* infection. Poor performance status was the only identifiable factor associated with an increased incidence of bacteremia. The surveillance study showed that significantly fewer bacterial strains were resistant to ofloxacin than to co-trimoxazole and that acquisition of resistance to co-trimoxazole was more commonly observed than was acquisition of resistance to ofloxacin. Significantly more patients had skin rashes following co-trimoxazole than ofloxacin treatment ($P < 0.05$). Ofloxacin was superior to co-trimoxazole in preventing infection in this population of neutropenic patients.

Infection is a frequent consequence of severe neutropenia (9). In the treatment of hematological malignancies such as leukemia and lymphoma, periods of neutropenia are induced by cytotoxic chemotherapy. The risk of infection is further enhanced by the toxicities of the cytotoxic drugs to the mucous membranes of the oral cavity and the gastrointestinal tract. Many of these infections are caused by endogenous enteric organisms (6).

Various studies have shown the efficacy of protective isolation and prophylactic oral antibiotics in preventing neutropenic infections (6). Combinations of oral, nonabsorbable antibiotics aimed at total gastrointestinal decontamination are often poorly tolerated by patients and may encourage the acquisition of resistant organisms (6, 9). The alternative approach of selective gastrointestinal decontamination aims to eliminate the aerobic flora of the gut but to preserve the anaerobic flora, and hence, the colonization resistance of the host is maintained (6). Co-trimoxazole is a popular drug for this purpose and has been shown to be effective in reducing the incidences of bacterial as well as *Pneumocystis carinii* infections in neutropenic patients (2, 7). However, side effects such as gastrointestinal disturbance and skin rash are not infrequently associated with co-trimoxazole, and the emergence of organisms resistant to the drug is also troublesome (9). Up to 26% of the *Escherichia coli* isolates isolated from blood cultures in our hospital were resistant to co-trimoxazole (unpublished data). There is also evidence which suggests that co-trimoxazole may delay marrow recovery following intensive cytotoxic chemotherapy (13). Our Chinese patient population has the additional problem of a high incidence of glucose 6-phosphate dehydrogenase deficiency, which is a contraindication to the use of co-trimoxazole (5).

Recent studies on the newly available quinolone family of antibiotics, which possesses a wide spectrum of antibacterial activity and can be given orally, suggest that they are potentially useful in preventing neutropenic infections (4, 8, 14). In the present study we evaluated the efficacy of ofloxacin, a fluorinated quinolone, in comparison with that of co-trimoxazole in preventing infection in neutropenic patients following cytotoxic chemotherapy.

MATERIALS AND METHODS

Patients with hematological malignancies who were treated in the University Department of Medicine, Queen Mary Hospital, were eligible for participation in the study. Criteria for entry of patients into the study included (i) a neutrophil count of less than 0.5×10^9/liter after receiving cytotoxic chemotherapy; (ii) no clinical or microbiological evidence of infection; (iii) no antimicrobial therapy within 72 h prior to entering the study; (iv) no allergy to nalidixic acid, ofloxacin, or co-trimoxazole; and (v) normal glucose 6-phosphate dehydrogenase activity. Patients with severe hepatic or renal impairment (serum bilirubin, >50 μmol/liter; serum creatinine, >0.3 mmol/liter) were excluded. Patients were excluded from the study if they had a second neutropenic episode.

Initial assessment included history and physical examination, full blood counts, blood biochemistry, chest radiograph, and glucose-6-phosphate dehydrogenase activity. The performance scores of patients were assessed by standard criteria (15). Patients were randomized to receive either (i) co-trimoxazole, two tablets (each tablet contained 400 mg of sulfamethoxazole and 80 mg of trimethoprim) orally twice daily, or (ii) ofloxacin (Daiichi, Tokyo, Japan), 300 mg orally twice daily. All patients also received chlorhexidine mouthwash and nystatin suspension, 500,000 units orally four times daily. Patients who received induction chemotherapy for acute leukemia were managed as inpatients, with reverse

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isolation during the period of neutropenia. The remaining patients were allowed to receive therapy as outpatients, provided that their home environments were satisfactory. All patients received advice on diet and personal hygiene (6, 9). Outpatients were seen at least weekly in the clinic. Full blood counts, blood biochemistry, and chest radiography were done at least once every week. All patients were monitored for compliance, occurrence of infection, and drug-related side effects. Outpatients were instructed to report to the hospital immediately when they developed symptoms suggesting infection.

Patients who developed fever (two oral temperatures above 38°C at least 4 h apart within a 24-h period or a single oral temperature above 38.5°C) related to documented or suspected infection were admitted. The oral prophylactic antibiotic (co-trimoxazole or ofloxacin) was discontinued. Broad-spectrum intravenous antibiotics were commenced immediately after appropriate samples of blood, sputum, urine, throat swab, stool, and other appropriate specimens were taken for culture. Other investigations included complete blood counts, blood biochemistry, and chest radiograph. Invasive diagnostic procedures (e.g., bronchoscopy) were performed when indicated. For patients who developed no infection, oral prophylactic antibiotic (co-trimoxazole or ofloxacin) was discontinued when the neutrophil count reached $>0.5 \times 10^9$/liter or when an adverse reaction occurred. Only the infections that occurred while the patients were on the oral therapy and prior to the initiation of parenteral antibiotics were scored.

All patients had a surveillance culture of a rectal swab performed at the time of randomization and then weekly during the study period and after completion of the study. The swabs were inoculated onto MacConkey agar (Oxoid Ltd., Basingstoke, England) and were incubated at 37°C for 24 h. From plates that showed positive growth, up to 20 single colonies were randomly picked for identification by routine microbiological methods. The antimicrobial susceptibility studies of the bacterial isolates were performed by agar dilution by using the break-point method. The break-point for co-trimoxazole was set onefold higher than the usual recommendation, i.e., 8 μg/ml, while that for ofloxacin was set at 2 μg/ml, according to the recommendation of the manufacturer.

Informed consent was obtained from all patients. The protocol was approved by the Ethical Committee of the Faculty of Medicine, University of Hong Kong.

The response rates were expressed with confidence intervals (CI) (12). Chi-square analysis with the Yates' correction was used to compare the incidences of infections and toxicities and the various determining factors. The two-tail Z test was used to compare the results of the surveillance cultures.

RESULTS

During a 20-month period (September 1986 to April 1988), 110 eligible patients entered into the study and were randomized. Eight patients were excluded from the study. This was because of a history of allergy to co-trimoxazole in two patients, poor compliance in two patients (both received ofloxacin), and glucose 6-phosphate dehydrogenase deficiency in four patients, leaving 102 evaluable patients. A total of 52 patients received co-trimoxazole and 50 patients received ofloxacin. The patient characteristics are given in Table 1 and were comparable between the two groups.

A total of 25 of the 52 patients (48%; 95% CI, 35 to 61%) who received co-trimoxazole and 11 of the 50 patients (22%; 95% CI, 13 to 35%) who received ofloxacin developed fever during the study period. The types of infection and the causative organisms are summarized in Table 2. Gram-negative bacteremia occurred in nine patients in the co-trimoxazole group (17%; 95% CI 9 to 29%) but in only one patient (2%; 95% CI, 0 to 10%) in the ofloxacin group ($P < 0.05$).

TABLE 1. Patient characteristics[a]

Characteristic	Co-trimoxazole group (n = 52)	Ofloxacin group (n = 50)
Sex		
Female	20 (38)	19 (38)
Male	32 (62)	31 (62)
Median age (yr)	39	36
Age range (yr)	15–75	12–78
Performance score (WHO[b])		
0	41 (79)	40 (80)
1	10 (19)	7 (14)
2	1 (2)	3 (6)
Inpatients	26 (50)	26 (52)
Outpatients	26 (50)	24 (48)
Underlying primary disease		
Acute myeloid leukemia	27 (52)	25 (50)
Acute lymphoid leukemia	5 (10)	6 (12)
Malignant lymphoma	20 (38)	19 (38)
Primary disease status:		
At diagnosis	15 (29)	16 (32)
In remission	17 (33)	14 (28)
At relapse	20 (38)	20 (40)
Steroid therapy		
Yes	34 (65)	37 (74)
No	18 (35)	13 (26)
Indwelling central venous catheter		
Yes	7 (13)	8 (16)
No	45 (87)	42 (84)
Nadir neutrophil count (10^6/liter)		
Mean ± SEM	180 ± 13.2	170 ± 12.9
Range	10–380	10–410
Days of neutropenia ($<0.5 \times 10^9$/liter) (no.)		
Mean ± SEM	15.8 ± 1.1	14.9 ± 1.2
Range	7–26	7–30

[a] Unless otherwise indicated, values are numbers (percentages) of patients.
[b] WHO, World Health Organization.

Of the 10 organisms that were recovered from the blood of the bacteremic patients, 9 were resistant in vitro to co-trimoxazole but susceptible to ofloxacin. The exception was the strain of *Pseudomonas aeruginosa* isolated from a patient who received ofloxacin, which was resistant to both antibiotics.

A total of 4 of the 25 infective episodes (16%; 95% CI, 6 to 35%) were fatal in the co-trimoxazole group, and 2 of the 11 infective episodes (18%; 95% CI, 5 to 48%) were fatal in the ofloxacin group (P was not significant).

Factors affecting the incidence of bacteremia were analyzed and are given in Table 3.

Table 4 shows the results of the surveillance culture, and

TABLE 2. Types of infection and the causative organisms

Infection type and causative organism	No. in[a]: Co-trimoxazole group (n = 52)	No. in[a]: Ofloxacin group (n = 50)	P value
Documented infection			
Bacteremia	9	1	<0.05
Escherichia coli	4	0	
Pseudomonas aeruginosa	2	1	
Klebsiella pneumoniae	2	0	
Aeromonas hydrophila	1	0	
Pneumonia caused by an unknown organism	2	2	NS[b]
Dental sepsis	1	0	NS
Disseminated chickenpox	0	1	NS
Disseminated fungal infection	1	2	NS
Fever with unknown source of infection	12	5	NS

[a] A total of 25 patients in the co-trimoxazole group and 11 patients in the ofloxacin group became infected ($P < 0.025$).
[b] NS, Not significant.

Table 5 shows the change in susceptibility of the organisms during the study.

Gastrointestinal upset was the most common side effect and was present in 10 of the 52 (19%) patients in the co-trimoxazole group and 8 of the 50 patients (16%) in the ofloxacin group (P was not significant). Skin rash was seen in eight patients (15%) in the co-trimoxazole group and in one patient (2%) in the ofloxacin group ($P < 0.05$). One patient with severe gastrointestinal upset following co-trimoxazole treatment and all patients with skin rash required discontinuation of the antimicrobial agents.

DISCUSSION

Prophylactic use of some members of the quinolone family in the prevention of neutropenic infections has been studied. Norfloxacin has been shown to be more effective than placebo, vancomycin-polymyxin, or co-trimoxazole for the prevention of gram-negative infections in three studies (1, 8, 14). Another clinical trial has also shown that ciprofloxacin is more effective than co-trimoxazole plus colistin in reducing the incidence of gram-negative bacillary infection (4).

Ofloxacin is another orally administered quinolone which is active against most gram-negative, many gram-positive, and some anaerobic bacteria (10). The relative resistance of anaerobic organisms to the quinolones may be valuable in preserving the gut colonization resistance (11). Ofloxacin has a distinctive pharmacokinetic profile in comparison to the other quinolones. The drug is rapidly absorbed orally, producing a high peak concentration in serum (several times higher than that of ciprofloxacin). Moreover, ofloxacin achieves high concentrations in most tissues and body fluids. The drug is well tolerated by patients and has few side effects (10).

In this study ofloxacin was shown to be more effective than co-trimoxazole in reducing the overall incidence of fever and infection in our neutropenic patients following cytotoxic chemotherapy. The incidence of gram-negative bacteremia was significantly reduced in the ofloxacin group. The observed difference in the incidences of gram-negative bacteremia could still be explained by the difficulty in recovering the bacteria in the blood following the use of ofloxacin. However, there seemed to be no corresponding increase in the incidence of unexplained fever, but the number of these episodes in this study was too small to make a definite conclusion.

As none of our patients had a documented gram-positive bacterial infection, the effectiveness of ofloxacin in preventing gram-positive sepsis was unable to be determined from the results of this study. Only 15% of our patients had indwelling central venous catheters, which are known to be associated with an increased incidence of gram-positive bacterial infections (1). The incidence of nonbacterial infections appeared to be similar in both groups of patients. In contrast to ofloxacin, co-trimoxazole has been shown to be effective in preventing *P. carinii* infection (4). However, this effect could not be demonstrated in this study because of the

TABLE 3. Factors affecting the incidence of bacteremia in neutropenic patients

Characteristic	No. with incidence of infection/total no. tested (%)	P value
Sex		
Female	4/39 (10)	NS[a]
Male	6/63 (10)	
Age		
<40 yr	4/52 (8)	NS
>40 yr	6/50 (12)	
Performance score (WHO[b])		
0	5/81 (6)	<0.05
1, 2	5/21 (24)	
Inpatient	7/52 (13)	NS
Outpatient	3/50 (6)	
Underlying primary disease		
Acute myeloid leukemia	6/52 (12)	NS
Acute lymphoid leukemia or malignant lymphoma	12/50 (24)	
Primary disease status		
At diagnosis or relapse	9/71 (13)	NS
In remission	1/31 (3)	
Steroid therapy		
Yes	7/71 (10)	NS
No	3/31 (10)	
Indwelling central venous catheter		
Yes	3/15 (20)	NS
No	7/87 (8)	
Nadir neutrophil count (10^9/liter) of:		
>0.1	6/62 (10)	NS
<0.1	4/40 (10)	
Days of neutropenia (<0.5 × 10^9/liter)		
>14	7/53 (13)	NS
<14	3/49 (6)	

[a] NS, Not significant.
[b] WHO, World Health Organization.

TABLE 4. Susceptibility of gram-negative bacilli isolated from rectal swabs (surveillance culture)

Organism	Total no. of strains	No. of strains (%) resistant to:		P value
		Co-trimoxazole	Ofloxacin	
Escherichia coli	1,619	651 (40.2)	Nil	<0.0001
Klebsiella or *Enterobacter* spp.	201	55 (27.4)	Nil	<0.0001
Edwardsiella spp.	76	69 (90.8)	Nil	<0.0001
Proteus spp.	25	7 (28.0)	Nil	<0.05
Citrobacter spp.	19	5 (26.3)	Nil	<0.02
Salmonella spp.	2	Nil	Nil	NS[a]
Gram-negative bacilli[b] (glucose nonfermenting)	40	8 (20.0)	Nil	<0.003
Others	164	70 (42.7)	Nil	<0.0001
Total	2,146	865 (40.3)	Nil	<0.001

[a] NS, Not significant.
[b] Included *Pseudomonas*, *Alcaligenes*, *Achromobacter*, and *Eikenella* spp.

absence of documented cases. There was, however, no evidence to suggest that patients who received ofloxacin had a relative increase in the incidences of gram-positive or nonbacterial infections. A heterogeneous group of patients was included in this study. Poor performance status was the only identifiable factor associated with a significantly increased incidence of bacteremia (Table 3).

The surveillance cultures of the rectal swabs of our patients showed that significantly fewer strains ($P < 0.0001$) of gram-negative bacilli were resistant to ofloxacin than to co-trimoxazole (Table 4). Furthermore, acquisition of strains that were resistant to co-trimoxazole during the study period appeared to be more commonly observed than did acquisition of strains that were resistant to ofloxacin (Table 5). However, as some of the strains isolated by day 7 may have been colonizing the gut from day 1, the actual increase in the number of resistant bacteria could not be determined with certainty.

Similar incidences of gastrointestinal disturbance were observed following co-trimoxazole and ofloxacin treatment. However, it was difficult to determine the contribution of the oral antibiotics to the gastrointestinal side effects, which could also have been related to the cytotoxic chemotherapy given to the patients. However, skin rashes were more commonly associated with co-trimoxazole ($P < 0.05$).

The effect of co-trimoxazole on marrow recovery could not be assessed in this study because of the heterogeneity of the patients. The duration of neutropenia, however, was not different between the two groups.

The prophylactic oral administration of ofloxacin to our neutropenic patients was more effective than co-trimoxazole administration in reducing the incidence of gram-negative bacillary infection, probably as the result of suppression of gastrointestinal colonization by enteric pathogens, which could cause subsequent systemic infections during the period of neutropenia. This reflected the high incidence of resistance of these pathogens to co-trimoxazole. Ofloxacin was well tolerated by our patients and did not appear to predispose them to the emergence of resistant bacteria (3). However, there is considerably less experience with ofloxacin, and it is possible that the problem of resistance may emerge with more widespread use of the drug. These results suggest that ofloxacin is a promising drug for the prevention of neutropenic infections. Whether it is superior to other quinolones remains to be determined by further clinical trials.

TABLE 5. Susceptibility of gram-negative bacilli isolated from rectal swab (surveillance culture) before and after 7 days of antibiotics

Day	Total no. of strains	No. of strains (%) resistant to:	
		Co-trimoxazole	Ofloxacin
0	1,331	324 (24.3)	Nil
7	815	541 (66.4)	Nil
P value		<0.0001	NS[a]

[a] NS, Not significant.

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LITERATURE CITED

1. **Bow, E. J., E. Rayner, and T. J. Louie.** 1988. Comparison of norfloxacin with cotrimoxazole for infection in acute leukaemia. Am. J. Med. **84**:847–854.
2. **Bow, E. J., E. Rayner, B. A. Scott, and T. J. Louie.** 1987. Selective gut decontamination with nalidixic acid or trimethoprim-sulfamethoxazole for infection prophylaxis in neutropenic cancer patients: relationship of efficacy to antimicrobial spectrum and timing of administration. Antimicrob. Agents Chemother. **31**:551–557.
3. **Crumplin, G. C., and M. Odell.** 1987. Development of resistance to ofloxacin. Drug **34**(Suppl. 1):1–8.
4. **Dekker, A. W., M. Rozenberg-Arska, and J. Verhoef.** 1987. Infection prophylaxis in acute leukaemia: a comparison of ciprofloxacin with trimethoprim-sulfamethoxazole and colistin. Ann. Intern. Med. **106**:7–12.
5. **Grahame-Smith, D. G., and J. K. Aronson.** 1984. The Oxford textbook of clinical pharmacology and drug therapy, p. 126–131. Oxford University Press, Oxford.
6. **Hann, I. M., and H. G. Prentice.** 1984. Infection prophylaxis in the patient with bone marrow failure. Clin. Haematol. **13**: 523–548.
7. **Hughes, W. T., G. K. Rivera, M. J. Schell, D. Thornton, and L. Lott.** 1987. Successful intermittent chemoprophylaxis for Pneumocystis carinii pneumonitis. N. Engl. J. Med. **316**:1627–1632.
8. **Karp, J. E., W. G. Merz, C. Hendricksen, B. Laughon, T. Redden, B. J. Bamberger, J. G. Bartlett, R. Saral, and P. J. Burke.** 1987. Oral norfloxacin for prevention of gram negative bacterial infections in patients with acute leukaemia and granulocytopenia. Ann. Intern. Med. **106**:1–7.
9. **Marcus, R. E., and J. M. Goldman.** 1986. Management of infection in the neutropenic patient. Br. Med. J. **293**:406–408.
10. **Monk, J. P., and D. M. Campoli-Richards.** 1987. Ofloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs **33**:346–391.
11. **Pecquet, S., A. Andremont, and C. Tancrede.** 1987. Effect of oral ofloxacin on fecal bacteria in human volunteers. Antimicrob. Agents Chemother. **31**:124–125.
12. **Simon, R.** 1986. Confidence intervals for reporting results of clinical trials. Ann. Intern. Med. **105**:429–435.
13. **Wade, J. E., C. A. de Jongh, K. A. Newman, J. Crowley, P. H. Wiernik, and S. C. Schimpff.** 1983. Selective antimicrobial modulation as prophylaxis against infection during granulocytopenia: trimethoprim-sulfamethoxazole vs. nadidixic acid. J. Infect. Dis. **147**:624–634.
14. **Winston, D. J., W. G. Ho, S. L. Nakao, R. P. Gale, and R. E. Champlin.** 1986. Norfloxacin versus vancomycin/polymyxin for prevention of infections in granulocytopenic patients. Am. J. Med. **80**:884–890.
15. **World Health Organization.** 1979. Handbook for reporting cancer treatment. WHO offset publication no. 48. World Health Organization, Geneva.