Intensive Care Med (1998) 24: 1327–1330

BRIEF REPORT

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Outbreaks of *Staphylococcus aureus* infections during treatment of late onset pneumonia with ciprofloxacin in a prospective, randomized study

Received: 4 August 1998
Accepted: 27 August 1998

The study was supported by the BAYER AG

The results were presented at the 37 th Interscience Conference of Antimicrobial Agents and Chemotherapy 1997 in Toronto, Canada

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Abstract We carried out a prospective, randomized four-center study in nosocomial pneumonia to evaluate the clinical and microbiological efficacy and safety of different treatment regimens in adult intensive care patients. During the randomized treatment of 18 patients with late onset pneumonia, ciprofloxacin (CIP) was compared to ceftazidim plus gentamicin (CAZ/GM), outbreaks of *Staphylococcus aureus* infections occurred in center 1. This article reports the unexpected findings.
In the CIP group six out of ten patients were superinfected or reinfected with ciprofloxacin-resistant pathogens at the follow-up on day 5 after treatment. Four out of these six patients were superinfected with methicillin-susceptible or methicillin-resistant *S. aureus* (MRSA). Four superinfected patients died with pneumonia during treatment or before the follow-up. In the CAZ/GM group one out of eight patients was superinfected with MRSA. One patient died with pneumonia during treatment. There was no problem with multiresistant *S. aureus* or MRSA before the study period in center 1.
In conclusion, we observed outbreaks of *S. aureus* infections during the treatment of late onset pneumonia with ciprofloxacin, which were associated with a high mortality. These superinfections occurred in mechanically ventilated, postoperative cardiac surgical patients after 13 days in the intensive care unit (ICU). We recommend combining ciprofloxacin with an antibiotic agent active against gram-positive bacteria in ventilator-associated pneumonia after a prolonged ICU stay. Selective pressure of ciprofloxacin could have played a role in these superinfections.

Key words Nosocomial pneumonia · *S. aureus* · Superinfection · Ciprofloxacin

Introduction

Nosocomial pneumonia is the most frequent nosocomial infection in intensive care units (ICU) with a mortality rate of 30–70 % of the patients affected [1]. Our decision to compare different treatment regimens for early and late onset or consecutive pneumonia was based on the retrospective analysis of the data of 300 adult intensive care patients with nosocomial pneumonia in one of the ICUs in Bremen. This analysis showed that, after a stay of more than 5 days, the causative pathogens changed from bacteria known to be responsible for community-acquired pneumonia in early onset pneumonia to gram-negative Enterobacteriaceae, *Pseudomonas* species and

other non-fermenters in late onset or consecutive pneumonia. No local problems with multiresistant or methicillin-resistant *Staphylococcus aureus* (MRSA) were identified before the study period. We will report only the clinical and microbiological results of the treatment for late onset pneumonia with ciprofloxacin (CIP) versus ceftazidim (CAZ) plus gentamicin (GM) in center 1. The results of the statistical analysis of superinfections and the overall mortality in the intent-to-treat collective (entire study) of the CIP and CAZ/GM groups will be reported, too. In center 1 we analyzed retrospectively the doses of ciprofloxacin used in 1993–1996 and correlated them to the emergence of multiresistant *S. aureus* and MRSA.

Patients and methods

The study was approved by the Ethical Committees of the hospitals of Bremen and of the Berlin Medical Association, and was carried out in 1995. The study population consisted of adult intensive care patients in three teaching hospitals. Patients who met the enrollment criteria were stratified and randomized. For early onset pneumonia, mezlocillin plus sulbactam was compared to cefotiam. In cases of insufficient initial therapy, late onset or consecutive pneumonia, 0.4 g ciprofloxacin t.i.d. was compared to 2 g ceftazidim t.i.d. plus 5 mg/kg body weight gentamicin once daily. Late onset pneumonia was defined as pneumonia which occurred after day 5 of a hospital stay. The enrollment criteria were oriented to the CDC criteria for nosocomial pneumonia. Important exclusion criteria were: treatment with one or more of the study drugs within the 14 days prior to enrollment (except perioperative antibiotic prophylaxis) and any concomitant systemic antibacterial treatment and pathogens known to be resistant against the study drugs. Prior to and twice-weekly during treatment, and on day 1 and day 5 after the termination of the antibiotic treatment the patients underwent clinical, laboratory, radiological and microbiological evaluations. With the clinical assessments on day 1 and day 5 after treatment the patients were classified as responders if the clinical signs and symptoms related to the infection disappeared or improved, and as non-responders if insufficient reduction of the signs and symptoms of infection made additional therapy necessary.

With the first microbiological assessment on day 1 the efficacy of treatment on the primary pathogens was evaluated and classified as elimination (disappearance of the pre-therapy organism), presumed elimination (if no material was available), elimination with recurrence and persistence (in cases of continued isolation of the causative pathogen). With the second microbiological assessment the appearance of new pathogens during and after the antibiotic treatment was evaluated. The acquisition of a new pathogen requiring treatment during study therapy was classified as superinfection and the acquisition of a new pathogen requiring treatment before day 5 as reinfection. In cases of death during treatment or before day 5, the last specimen was used for the microbiological assessments. The specimens for all microbiological evaluations were gained by bronchoscopic broncho-alveolar lavage. The bacterial susceptibility to the study drugs was measured as the minimal inhibitory concentration (MIC) by the broth dilution test.

Differences between treatment groups with critical probability values of 0,05 or less were considered statistically significant. Superinfections were compared using an exact version of Wilcoxon's rank sum test on the basis of the intent-to-treat collective. The mortality rates of the treatment groups were compared using Fisher's exact test. All patients who received at least one dose of the study drug were included in the intent-to-treat collective. In center 1 we analyzed retrospectively the number of ciprofloxacin doses used per 1,000 patient-days in 1993–1996. They were correlated to the rates of ciprofloxacin-resistant *S. aureus* and MRSA out of all *S. aureus* isolates detected per 1,000 patient-days.

Results

Center 1

Ten patients were randomized to the CIP group and eight patients to the CAZ/GM group. Sixteen out of these 18 patients were enrolled for late onset pneumonia, two patients were non-responders to treatment for early onset pneumonia. These predominantly postoperative cardiac surgical patients were all on mechanical ventilation. They had a comparable severity of illness with a mean APACHE II score of 21 (SD ± 4 vs 5, respectively) at randomisation, a mean age of 64 years (SD ± 8 vs 9, respectively) and a median hospital stay of 14 days (range 7–63) in the CIP group and 16 days (range 7–30) in the CAZ/GM group at enrollment.

The clinical outcome

In the CIP group two out of ten patients were cured at the follow-up on day 5. Eight patients died. Five patients died during treatment or before day 5, four of them with pneumonia. In the CAZ/GM group four out of eight patients were cured on day 5. Four patients died. Two patients died during treatment or before day 5, one of them with pneumonia.

The microbiological results

At the first microbiological assessment after treatment the causative pathogens were eliminated or presumed eliminated in both groups except one persistent *P. aeruginosa* in the CAZ/GM group, which was only colonising. At the second microbiological assessment after treatment six out of ten patients in the CIP group were superinfected or reinfected. Four patients were superinfected with *S. aureus*, two strains were methicillin-resistant, all strains were ciprofloxacin-resistant (MICs of 16–32 μg/ml). One patient was superinfected with C*orynebacterium xerosis* and one patient was reinfected with *P. aeruginosa*. All pathogens, which caused superinfections and reinfections appeared for the first time in these patients and were ciprofloxacin-resistant. In the CAZ/GM group one patient was superinfected with MRSA (ciprofloxacin-susceptible). The superinfections occurred during therapy on day 5 (mean value; SD ± 3) and after a mean ICU stay of 13 ± 4 days. The results of the second micro-

Table 1 Casewise listing of all superinfections and reinfections and clinical outcome in the ciprofloxacin group and ceftazidim/gentamicin group in center 1

No.	Organism specified	Microbiological result	Clinical assessment		Outcome
			day 1	day 5	
Ciprofloxacin group (n = 10)					
67	*S. aureus* (MSSA)	Superinfection	Failure	Death with pneumonia	Death
70	*S. aureus* (MSSA)	Superinfection	Death with pneumonia		Death
132	*S. aureus* (MRSA)	Superinfection	Failure	Death with pneumonia	Death
133	*Corynebacterium xerosis*	Superinfection	Death with pneumonia		Death
137	*S. aureus* (MRSA)	Superinfection	Failure		Death on day 14
138	*P. aeruginosa*	Reinfection	Failure		Death on day 33
Ceftazidim/gentamicin group (n = 8)					
68	*S. aureus* (MRSA)	Superinfection	Failure		Survivor

biological assessment after treatment and the clinical outcome are shown in a casewise listing (Table 1) of all superinfections and reinfections in center 1.

In the years 1993–1995 the number of *S. aureus* isolates per 1,000 patient-days in the center was 39, 45 and 42, respectively. In 1996 it increased to 65 due to epidemic nosocomial MRSA-infections. Standard susceptibility testing of all *S. aureus* isolates included ciprofloxacin and oxacillin. In 1993 and 1994 only 3 (7%) out of all *S. aureus* per 1,000 patient-days were ciprofloxacin- and methicillin-resistant. In the study year 1995 the number increased to 9 (21%) and in 1996 to 16 (25%) ciprofloxacin-resistant *S. aureus* and 14 (22%) MRSA. Copy-strains were not eliminated. The ciprofloxacin doses used per 1,000 patient-days decreased from 120 in 1993 and 1994 to 80 in 1995 and 70 in 1996. Only patients with an ICU stay of more than 48 h were evaluated.

Statistical results of the patients enrolled overall in the CIP and the CAZ/GM group (four centers)

The intent-to-treat collective of the entire study consisted of 28 patients in the CIP group and 23 patients in the CAZ/GM group. Seven out of 28 patients were superinfected in the CIP group, five out of seven patients in center 1. One out of 23 patients was superinfected in the CAZ/GM group. This was a highly significant difference ($p < 0.0002$). The overall mortality in the CIP and CAZ/GM groups was 37%, 19 out of 51 patients died. Thirteen (46%) out of 28 patients died in the CIP group and six (26%) out of 23 patients in the CAZ/GM group. The difference was not significant from a statistical point of view ($p < 0.15$). The study was terminated due to low overall enrollment.

Discussion

Reports have been published about the rapid development of ciprofloxacin resistance in *S. aureus* and *P. aeruginosa* [2, 3]. Sporadic emergence of resistance during the course of therapy has been reported to occur both in infections caused by methicillin-susceptible *S. aureus* (MSSA) and MRSA [4] from the outset of clinical trials. However, the superinfections which occurred during ciprofloxacin therapy in center 1 were unexpected. These superinfections were caused predominantly by multiresistant and methicillin-resistant *S. aureus* although the rate of these pathogens was small in the pre-study period in center 1. The ciprofloxacin doses used per 1,000 patient-days decreased by one third in the study year 1995, but the rate of ciprofloxacin- and methicillin-resistant *S. aureus* tripled. Selective pressure of ciprofloxacin could have played a role in the superinfections and the increasing rate of ciprofloxacin-resistant *S. aureus* and MRSA. The strains were not typed in 1993–1995. In 1996 and 1997 outbreaks of nosocomial MRSA infections with a single clonal epidemic strain occurred in our ICU. This strain showed the same pattern of resistance as the MRSA which caused the superinfections during ciprofloxacin therapy.

In conclusion, we observed outbreaks of *S. aureus* infections in postoperative cardiac surgical patients during the treatment of late onset pneumonia with ciprofloxacin after mechanical ventilation for 13 days. These outbreaks were associated with a high mortality. We recommend not to use ciprofloxacin in cases of ventilator-associated pneumonia without an antibiotic agent active against gram-positive pathogens if the patient has already been in the ICU for several days.

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