Cefonicid ‘restores’ the depressed activities of polymorphonuclear cells from chronic haemodialysis patients and renal transplant recipients in vitro

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Abstract

Background. Chronic haemodialysis patients and renal transplant recipients are highly susceptible to infection characterized by high morbidity and mortality and related to an impairment of the phagocytic response.

Subjects and methods. In order to elucidate how cefonicid, a cephalosporin with a broad spectrum of activity and once-daily dosage, influences this phagocytic response, the effects of the drug upon the functions of human PMNs from both healthy individuals and immunocompromised patients were investigated.

Results. In vitro, PMNs from haemodialysed patients and renal transplant recipients showed a diminished phagocytic efficiency with reduced phagocytosis and bactericidal activity towards intracellular Klebsiella pneumoniae when compared with that seen in PMNs from healthy subjects. Cefonicid significantly affected the activity of PMNs from healthy volunteers, resulting in either an increased percentage of ingested klebsiellae or a reduced intracellular bacterial load when compared with the control, drug-free system. When cefonicid was added to PMNs from uraemic patients a pattern similar to that observed with phagocytes from healthy subjects was detected: the antibiotic was able to ‘restore’ the depressed primary functions of PMNs, resulting in a significant increase in both phagocytosis and killing activity.

Conclusions. Cefonicid, with its several immunoproperties observed in this study, possesses interesting beneficial properties which make it suitable for the treatment of infections in patients with impaired components of the immune system.

Key words: Cefonicid; K. pneumoniae; human polymorphonuclear cells (PMNs); intraPMN killing activity; phagocytosis; uraemic patients

Introduction

The failure of antibiotic therapy is often related to the inability of the patient’s immune system to provide the support that antibiotics need for the eradication of the infection. Thus the modern trend in therapy requires drugs with a stimulatory effect rather than an immunosuppressive effect on the cells of the immune system be used, particularly when administered to immunocompromised patients. The literature reports evidence suggesting that many antimicrobial agents are able to modulate the host defences in different ways [1–7]. Among patients with defects of the phagocytic component of the immune system, chronic haemodialysis patients and renal transplant recipients are highly susceptible to infection characterized by high morbidity and mortality and related to an impairment of the phagocytic response [8–11]. The present study was designed to evaluate, in vitro, the potential effect of cefonicid, a cephalosporin with a broad spectrum of activity and once-daily dosage, on the functions of human polymorphonuclear cells (PMNs) from healthy volunteers, haemodialysed patients and renal transplant recipients against Klebsiella pneumoniae. Klebsiella pneumoniae is one of the major Gram-negative human pathogens isolated with relatively high frequency in hospital-acquired infections, which can pose severe problems in patients whose immunity is impaired.

Subjects and methods

Bacteria

A clinical strain of K. pneumoniae isolated from patients with symptomatic urinary tract infection was cultured to mid-exponential phase in Brain Heart Infusion broth (BHI; Unipath, Italy), concentrated 10× in BHI broth containing 30% glycerol, quick frozen in dry ice-ethanol and stored at −70°C.

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Cefonicid was kindly provided by SmithKline Beecham (Italy). The compound was dissolved in phosphate-buffered saline (PBS; 0.1 M, pH 7.4) immediately before each experiment. Antibiotic susceptibility testing was performed using the standardized dilution method in Mueller Hinton broth (Unipath) with an inoculum of $2 \times 10^5$ cfu/ml.

Subjects

All patients participating in this study gave their informed consent. Withdrawals were obtained from 45 healthy volunteers, as controls, and from 55 immunocompromised patients without any evidence of infection, followed at Dialysis Center of the Ivrea Hospital (Italy). The subjects were divided in two groups. The first group included 31 patients on haemodialysis: 17 males and 14 females ranging in age from 24 to 75 years (mean age 59.8 ± 12 years). The mean time on dialysis was 61.8 ± 53 months and the causes of ureaemia were as follows: chronic glomerulonephritis (7 cases), nephroangiosclerosis (8 cases), polycystic kidney disease (3 cases), diabetic nephropathy (3 cases), chronic renal failure (7 cases), renal neoplasia (1 case), and interstitial nephritis (2 cases). The mean normalized dose of dialysis per treatment ($KTV = 1.47 \pm 0.26$) and the protein catabolic rate (PCR = 1.1) indicate an adequate dialysis prescription and nutrition. About 60% of the patients had secondary hyperparathyroidism (mean plasma levels of iPTH for all patients was 214 pg/ml). The second group included 24 patients that had undergone renal transplantation: 17 males and 7 females, mean age 45.3 ± 10 years. The mean time since transplantation was 55.9 ± 49 months and primary renal diseases were as follows: chronic glomerulonephritis (9 cases), interstitial nephritis (5 cases), polycystic kidney disease (4 cases), diabetic nephropathy (2 cases), chronic renal failure (2 cases), other (1 case). The mean serum creatinine at the time of the study was 1.6 ± 0.7 mg/dl. Post-transplant immunosuppressive treatment in 13 patients was cyclosporine A (CyA) and prednisone (P); in 9 patients CyA, P and azathioprine (AZA); in 1 patient CyA and AZA and in 1 patient AZA and P.

Polymorphonuclear granulocytes (PMNs)

Peripheral venous blood was collected into sterile evacuated blood-collecting tubes containing lithium heparin (15 units LH/ml blood) and settled at room temperature by gravity for 30 min in 2.5% dextran (70 000 mol wt; Pharmacia S.p.A., Italy) in normal saline (1:1 ratio). The leukocyte-rich plasma supernatant was carefully layered on Ficol–Paque (Pharmacia) and then centrifuged twice at 160 g for 15 min; to obtain pure PMNs, residual erythrocytes were lysed by hypotonic shock for 30 s in sterile distilled water and then centrifuged further. After being counted in a Bürker cell counting chamber, the density of the PMNs was adjusted to $10^6$ cells/ml in PBS supplied with 1% glucose and 0.1% human albumin (Sigma); the PMNs were then placed in sterile plastic tubes, treated with RPMI 1640 (Gibco Laboratories, USA), supplemented with 10% fetal calf serum (FCS; Gibco) and incubated for various periods at 37°C in a shaking water bath (150 rpm). The viability was assayed by trypan blue exclusion and was greater than 95%; a viability test was carried out before and after each experiment. The time between the collection of blood and the beginning of the experiments did not exceed 3 h; the interval between PMNs harvest and the start of the experiments was less than 30 min.

Radioactive labelling protocol

Experiments were initiated by transferring 200 μl of the frozen culture into fresh BHI broth containing 150 μCi of $[^3H]$uracil (specific activity 1165.5 GBq/mmol; Du Pont de Nemours, NEN Products, Italy). Following 4 h growth at 37°C, the radiolabelled klebsiellae were centrifuged several times with BHI broth and resuspended in fresh medium to a final concentration of $2 \times 10^7$ cfu/ml, as confirmed by colony counts in triplicate.

Phagocytosis assay

Aliquots of 1.0 ml of klebsiellae ($2 \times 10^7$ cfu) in RPMI 1640 with 10% FCS, were added to PMNs in sterile plastic tubes (10^6 cells) and then incubated at 37°C in a shaking water bath. After incubation for 30–90 min the tubes were centrifuged at 160 g for 5 min; the pellet was then resuspended with phosphate saline and centrifuged at 160 g for 5 min to remove free klebsiellae. The cells were then resuspended in 1 ml of sterile distilled water for 5 min and 100 μl samples of this suspension were placed in scintillation fluid (Atomlight, NEN) and counted by liquid scintillation spectrometry. Radioactivity was expressed as c.p.m./sample. The percentage phagocytosis at a given sampling time [12] was calculated as:

$$\% \text{phagocytosis} = \left( \frac{\text{c.p.m. in PMN pellet}}{\text{c.p.m. in total bacterial pellet}} \right) \times 100$$

Measurement of antimicrobial activity of PMNs

Aliquots of 1 ml of klebsiellae ($2 \times 10^7$ cfu) and PMNs in sterile plastic tubes ($10^6$ cells) were incubated for 30 min in RPMI 1640 medium to allow phagocytosis to proceed. The PMN–bacteria mixtures were centrifuged at 160 g for 5 min and washed with phosphate saline to remove any free extracellular bacteria. Samples of the cells containing bacteria were lysed by adding sterile water and a viable count of intracellular klebsiellae was performed ($T_o$). The cells were then incubated further and at intervals ($T_i$) viable counts of surviving intracellular bacteria were measured in the same way. The PMN killing values were expressed as a Survival Index (SI), calculated as the number of surviving microorganisms at 30 min ($T_o$) plus the number of surviving microorganisms at $T_i$ divided by the number of surviving microorganisms at $T_o$ as follows [13]:

$$\text{SI} = \frac{(\text{No. of cfu at } T_o + \text{No. of cfu at } T_i)}{(\text{No. of cfu at } T_o)}$$

According to this formula, if 100% killing took place, the ratio would be 1.

Effect of cefonicid on PMN functions

The effects of cefonicid on PMN phagocytosis and intracellular killing of K. pneumoniae were investigated by incubating the bacteria and phagocytes at 37°C in a shaking water bath in the presence of half the minimal inhibitory concentration (MIC) of the drug. Each test was carried out in quadruplicate and compared with control systems which contained no antibiotics.
Influence of cefonicid on PMNs from uraemic patients

Statistical analysis

The results are expressed as the mean and standard error of 10 separate experiments. Statistical evaluation of the differences between test and control results were performed by an analysis of variance (ANOVA) using Tukey’s test.

Results

In all experiments the viability of PMNs remained unchanged throughout. The MIC of cefonicid against the strain of K. pneumoniae (2 × 10⁷ cfu/ml) was 16 μg/ml.

The results shown in Table 1 indicate a diminished phagocytic efficiency with reduced phagocytosis and bactericidal capacity in PMNs from immunosuppressed subjects (haemodialysed patients and renal transplant recipients) when compared with the healthy controls. In fact, PMNs from healthy subjects were able to engulf between 30.6% and 20.22% of the bacteria in 90 min of observation; by contrast, PMNs from haemodialysed and renal transplant patients showed a diminished bacterial ingestion (25–17.4% and 19.4–15.5% respectively; \( P < 0.01 \)). Moreover, considerable difference was found among the bactericidal abilities of PMNs from haemodialysed patients, renal transplant recipients and healthy subjects (Table 1). PMNs from uraemic patients were able to kill 50% of the ingested klebsiellae until 30 min only; after that time no killing occurred (SI > 2). On the contrary, the intracellular activity of PMNs from healthy subjects was present for the entire 90 min of observation (57–31%).

To determine the combined effect of phagocytes and cefonicid, K. pneumoniae was added to half the MIC of the drug in the presence of human PMNs (Table 2). The direct exposure of PMNs from healthy subjects, and klebsiellae to sub-inhibitory concentrations of cefonicid, significantly enhanced the phagocytosis, with an increased percentage of engulfed bacteria after 30 min of incubation (61.23 ± 2.8) and up to 90 min (76.88 ± 5.8) compared with the control, drug-free system (30.6 ± 2.6 and 20.22 ± 2.1 respectively; \( P < 0.01 \)).

Cefonicid always enhanced intracellular killing of phagocytosed klebsiellae by PMNs compared with controls. In the drug-free cultures the value of SI shifted from 1.43 at 30 min to 1.53 at 60 min and 1.69 at 90 min, which corresponds with a progressive increase in the number of intracellular bacteria. The presence of the antibiotic, however, produced a significantly higher killing effect (\( P < 0.01 \)) reducing the intracellular bacterial load by 89–90% (Table 2).

A similar pattern was detected with phagocytes from immunosuppressed subjects (Tables 3 and 4). The presence of half the MIC of cefonicid resulted in a statistically significant increase in bacterial uptake (\( P < 0.01 \)): in fact klebsiellae are phagocytosed at a rate that is ~3-fold of that of the drug-free controls and similar to that observed in healthy subjects. The bacterial killing of PMNs from immunosuppressed subjects also increased in the presence of cefonicid, achieving the same values seen with PMNs from healthy subjects, whereas in drug-free systems phagocytosed bacteria remained viable after 60 min: values of SI were greater than 2, indicating intracellular survival.

Discussion

In order to be effective against Gram-negative bacteria a \( \beta \)-lactam must possess a broad antibacterial spec-

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean % phagocytosis ± SEM</th>
<th>Survival Index ± SEM</th>
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<tbody>
<tr>
<td></td>
<td>Healthy subjects</td>
<td>Haemodialysed patients</td>
</tr>
<tr>
<td>30 min</td>
<td>30.60 ± 2.6</td>
<td>24.94 ± 3.7</td>
</tr>
<tr>
<td>60 min</td>
<td>24.12 ± 1.8</td>
<td>20.95 ± 1.1</td>
</tr>
<tr>
<td>90 min</td>
<td>20.22 ± 2.1</td>
<td>17.43 ± 3.6</td>
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% = Percentage of initial bacterial population killed by PMNs.

Table 2. Functional activity of PMNs from healthy subjects: phagocytosis and killing against K. pneumoniae in the presence of cefonicid

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean % phagocytosis ± SEM</th>
<th>Survival Index ± SEM</th>
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<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Cefonicid</td>
</tr>
<tr>
<td>30 min</td>
<td>30.60 ± 2.6</td>
<td>61.23 ± 2.8</td>
</tr>
<tr>
<td>60 min</td>
<td>24.12 ± 1.8</td>
<td>60.20 ± 3.6</td>
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<tr>
<td>90 min</td>
<td>20.22 ± 2.1</td>
<td>76.88 ± 5.8</td>
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*Significantly different (\( P < 0.01 \)) from the controls.
Table 3. Functional activity of PMNs from haemodialysed patients: phagocytosis and killing against *K. pneumoniae* in the presence of cefonicid

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mean % phagocytosis ± SEM</th>
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<tr>
<td>30</td>
<td>24.94 ± 3.7</td>
<td>48.8 ± 3.3</td>
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<tr>
<td></td>
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<tr>
<td>60</td>
<td>20.95 ± 1.1</td>
<td>59.4 ± 5.4</td>
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<td></td>
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<tr>
<td>90</td>
<td>17.43 ± 3.6</td>
<td>66.6 ± 5.7</td>
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*Significantly different (P < 0.01) from the controls.

Table 4. Functional activity of PMNs from renal transplant recipients: phagocytosis and killing against *K. pneumoniae* in the presence of cefonicid

<table>
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<tr>
<td></td>
<td>Controls</td>
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</tr>
<tr>
<td>30</td>
<td>19.43 ± 2.3</td>
<td>47.62 ± 4.9</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>60</td>
<td>19.8 ± 0.3</td>
<td>56.9 ± 6.6</td>
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<tr>
<td></td>
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<tr>
<td>90</td>
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<td>75.42 ± 5.4</td>
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Intracellular uptake by human macrophages and from immunosuppressed subjects also increased in the presence of cefonicid, achieving the values seen with the major cause of death, and is likely to be related to a high rate of infection is a frequent complication and the major cause of death, and is likely to be related to an impairment of the phagocytic response [8,11,21], the influence of cefonicid on the functions of PMN cells from uraemic patients towards *K. pneumoniae* was investigated.

PMNs from haemodialysed patients and renal transplant recipients showed a diminished *in vitro* phagocytic efficiency with reduced phagocytosis and bactericidal activity, compared with that seen in PMNs from healthy volunteers (Table 1). It is known that phagocytosis by PMNs plays an important defensive role against bacterial infections by the ingestion of micro-organisms, and their subsequent destruction by bactericidal mechanisms, namely the production of oxygen free radicals during the respiratory burst. As far as phagocytosis is concerned our findings conflict strongly with recent data obtained by Iida *et al.* [22], showing intact PMN phagocytic activity in chronic haemodialysis patients. To explain these discrepancies further investigations will be required. However, some previous studies have reported that in uraemic patients the number of PMNs is normal but several metabolic and functional alterations are observed [21,23,24]. Our results confirm these data and the reduction in host response mechanisms, observed in both haemodialysed patients and renal transplant recipients (Table 1), may therefore explain the high incidence of infection among patients with severe renal failure and dialysis.

When compared with the control, drug-free system, cefonicid, at half its MIC, significantly affected the activity of PMNs from healthy subjects against *K. pneumoniae in vitro*, resulting either in an increased percentage of ingested bacteria or in a reduced intracellular killing of PMNs from haemodialysed patients (Table 3) and renal transplant recipients (Table 4) a similar pattern was detected. The presence of half the MIC of the drug resulted in a significant increase in the bacterial uptake; klebsiellae were phagocytosed at a rate that was 3-fold that of the drug-free controls and similar to that observed in healthy subjects. The bacterial intracellular killing of PMNs from immunosuppressed subjects also increased in the presence of cefonicid, achieving the values seen with the major advantages of this antibiotic over other cephalosporins include its high serum levels and an extended elimination half-life of ~4.8 h which allows once-daily dosing [15]. According to the great majority of previous publications, cefalosporins, which are widely used in the treatment and prevention of bacterial infections, have no relevant effects on phagocyte functions [1]. However, in recent years, it has been reported that some cephalosporins are able to increase either phagocytosis or the killing of Gram-positive and Gram-negative bacteria by PMNs and mononuclear cells [16–18]. From our previous reports [19,20] it emerges that cefonicid combines good *in vitro* activity with the capacity to act in concert with the immune system in a way that potentiates the host’s defences. In fact, at sub-inhibitory concentrations, cefonicid significantly increases *in vitro* and *ex vivo* bactericidal uptake by human macrophages and intracellular activity towards phagocytosed *K. pneu-

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% = Percentage of initial bacterial population killed by PMNs in presence of the antibiotic.

trum, penetrate the outer membrane, be resistant to *β*-lactamases, bind to the penicillin-binding proteins (PBPs) and have the desired pharmacological activity [14]. Among cephalosporins, cefonicid, a second generation cephalosporin, possesses a broad spectrum of antibacterial activity, including against Gram-negative anaerobes. The major advantages of this antibiotic are its high serum levels and an extended elimination half-life of ~4.8 h which allows once-daily dosing [15]. According to the great majority of previous publications, cefalosporins, which are widely used in the treatment and prevention of bacterial infections, have no relevant effects on phagocyte functions [1]. However, in recent years, it has been reported that some cephalosporins are able to increase either phagocytosis or the killing of Gram-positive and Gram-negative bacteria by PMNs and mononuclear cells [16–18]. From our previous reports [19,20] it emerges that cefonicid combines good *in vitro* activity with the capacity to act in concert with the immune system in a way that potentiates the host’s defences. In fact, at sub-inhibitory concentrations, cefonicid significantly increases *in vitro* and *ex vivo* bactericidal uptake by human macrophages and intracellular activity towards phagocytosed *K. pneumoniae*, which is known to pose serious clinical problems.

While such additional effects on the immune system may be of secondary importance in patients with normal host defence mechanisms, they are of primary importance in patients with depression of the immune system. Since in patients with chronic renal failure the high rate of infection is a frequent complication and the major cause of death, and is likely to be related to an impairment of the phagocytic response [8,11,21], the influence of cefonicid on the functions of PMN cells from uraemic patients towards *K. pneumoniae* was investigated.

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PMNs from healthy subjects (Table 2), whereas in drug-free systems phagocytosed bacteria remained viable after 60 min: SIs were greater than 2, indicating intracellular survival (Tables 3, 4). Further experiments carried out with 4 × MIC and 2 × MIC of cefonicid (corresponding to the serum levels at 1 and 3 h after drug administration in patients with renal impairment) showed that the phagocytic activity of PMNs remained similar to that observed with half the MIC of the drug; on the contrary, under these experimental conditions the presence of cefonicid produced a significantly higher enhancement of intracellular killing, leading to a total elimination of bacteria from the intracellular compartment (data not shown). These results indicate that cefonicid is able to induce a stimulation of the depressed phagocytic response in PMNs from uraemic patients, probably by modulating the interaction between K. pneumoniae and PMNs, and possibly by causing alterations to the bacterium and thereby increasing its susceptibility to the phagocytic and microbicidal activities of PMNs. In fact, in the presence of cefonicid, the primary functions of PMNs from immunocompromised patients are ‘restored’ achieving a pattern similar to that observed in the phagocytes from healthy subjects.

It is also possible, however, that other mechanisms could be involved in this synergistic phenomenon. In fact an indirect effect on phagocytic activity via changes in bacteria can be ruled out in some of our preliminary clinical studies involving non-infected patients. Briefly, eight haemodialysed patients with no active or recent infection were treated for 10 days with cefonicid (2 g iv) in order to compare the effect of cefonicid in vivo. A placebo group (four patients) served as reference; to ensure standardization, blood samples were taken at the same time in each patient. The preliminary clinical data seem to indicate that cefonicid was able to induce a statistically significant increase in both depressed phagocytosis and intracellular microbicidal activity of PMNs, in contrast to placebo (data not shown). However, further studies to provide more direct evidence are still required. These data are difficult to compare with others since very few have been reported in the literature. However, our results agree with the recent findings of Vanholder et al. [24], who reported that cefozidine, a third generation cephalosporin, has biological-response-modifying properties being able to stimulate the phagocytosis of uraemic patients. At present no other drugs are available to correct the impaired functions of the phagocytic system.

In conclusion, taken together, these positive immunoproperties of cefonicid, additional to its intrinsic, excellent conventional antibacterial activities, make this cephalosporin suitable for the treatment of infections in patients with defects of the phagocytic components of the immune system. The therapeutic potential of these observations requires further investigation.

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