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Efficacy and safety of intravenous meropenem and tobramycin *versus* ceftazidime and tobramycin in cystic fibrosis ☆

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Abstract

Background: Cystic fibrosis (CF) is characterized by chronic bacterial broncho-pulmonary infection. Although intravenous (IV) antibiotic therapy is regarded as standard treatment in CF, only few randomised trials comparing different antibiotic compounds exist.
Methods: We report on a prospective multicenter interventional trial of IV meropenem (120 mg/kg/day) or IV ceftazidime (200–400 mg/kg/day), each administered together with IV tobramycin (9–12 mg/kg/day). Outcome measures were changes in lung function, microbiological sputum burden and blood inflammatory marker. Liver and renal function values were measured to assess safety.
Results: One hundred eighteen patients (59/59) were included into the study with the following indications: first infection of *P. aeruginosa* ($n=6$), acute pulmonary exacerbation ($n=34$) and suppression therapy of chronic *P. aeruginosa* colonization ($n=78$). Both treatments improved lung function measures, bacterial sputum burden and CRP levels with no differences between treatment groups observed. A significant higher elevation for alkaline phosphatase ($p<0.0001$) was observed for patients in the meropenem/tobramycin group.
Conclusions: IV antibiotic therapy in CF patients with meropenem/tobramycin is as effective as with ceftazidime/tobramycin regarding lung function, microbiological sputum burden and systemic inflammatory status. Hepato-biliary function should be monitored carefully during IV treatment, possibly important in CF patients with pre-existing liver disease.

Keywords: Cystic fibrosis; Ceftazidime; Meropenem; Tobramycin; Safety

1. Introduction

Respiratory infection results in progression of cystic fibrosis (CF) lung disease [1]. Although the use of intravenous (IV) antibiotic agents for the treatment of acute pulmonary exacerbations (APE) in CF patients has become clinical practice [2], no consensus exists concerning the exact regimen, duration or dosage of therapy [3]. Ceftazidime and tobramycin is usually considered first-line therapy [4] and results of larger trials of tobramycin regimens have been published [5,6].

Recently, Blumer et al. reported a randomised comparative trial that assessed the changes in pulmonary function, clinical score and sputum microbacterial burden in 102 CF patients receiving IV tobramycin with either meropenem or ceftazidime to treat an acute exacerbation of CF lung disease [7]. The authors concluded that both regimens improved pulmonary and clinical status and reduced sputum bacterial burden. They also reported that a larger proportion of patients receiving meropenem/tobramycin therapy demonstrated a satisfactory response in FEV1 [7]. In that study no

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blood samples were taken to assess the change in systemic inflammatory status or monitor safety parameters like liver and kidney function tests.

The goal of this prospective randomised multicenter study was to compare both efficacy and safety of the intravenous antibiotic combinations meropenem/tobramycin *versus* ceftazidime/tobramycin in these CF patients, where this therapy is widely used. Thus, differently to Blumer et al. [7], we included also chronically colonized CF patients that received routine intravenous antibiotic treatment and those patients that received the treatment for eradication of first *P. aeruginosa* infection.

2. Methods

2.1. Study design

This was a randomised prospective multicenter, open labelled, interventional study. The goal was to compare efficacy and safety of the antibiotic combinations meropenem/tobramycin (MER) *versus* ceftazidime/tobramycin (CEF) for treatment of *P. aeruginosa* infection in CF patients.

2.2. Patient groups

Patients with CF were recruited from June 1997 to September 1999. Indications for antibiotic treatment were defined as (1) suppression therapy for chronic infection with *P. aeruginosa* without exacerbation of pulmonary symptoms, (2) acute exacerbation of chronic pulmonary *P. aeruginosa* infection and (3) eradication of *P. aeruginosa* after its first detection in respiratory secretions. It was allowed to include patients more than one time if the interval between the treatments was at least 8 weeks. Length of the therapy was determined clinically, outcome parameters were measured before and after treatment.

Inclusion criteria were age older than five years for indications (1) and (2) and older than two years for indication (3), evidence for infection with *P. aeruginosa* and susceptibility of the bacterial strains to the administered antibiotics. Oral or inhalative antibiotic therapy had to be stopped at least five days prior to study begin. Exclusion criterion was usage of oral steroids or non-steroidal-anti-inflammatory therapy.

2.3. Treatment

The patients were randomised to IV treatment with meropenem (Meronem®; AstraZeneca, Wedel, Germany) plus tobramycin (Gernebcin®) or ceftazidime (Fortum®) plus tobramycin for two to three weeks.

Intravenous meropenem was administered by infusion at a dose of 120 mg/kg given divided into 3 daily doses (if bodyweight was > 50 kg, 2 g of meropenem were administered thrice a day), intravenous ceftazidime was given at 200–400 mg/kg per day given in two or three daily doses and intravenous tobramycin was given at a dose of 9–12 mg/kg per day in two doses. The dosage was adjusted after 4–7 days to obtain tobramycin trough levels of less than 2 mg/dl.

2.4. Clinical measures

Pulmonary function testing was performed before and after treatment (body plethysmography, Jaeger, Viasys healthcare, Würzburg, Germany). FEV1, FVC and forced expiratory flow 25% (MEF25%) were collected.

2.5. Bacteriological measures

Sputum samples for culture were collected from each patient before start of the treatment and after the end of the trial. Sputum samples were obtained by deep spontaneous expectoration or deep throat swabbing, if spontaneous expectoration did not produce any sputum. Specimens were transported on charcoal agar for *P. aeruginosa* and other microorganisms (Transgerm GO, Merck, Darmstadt, Germany). The number of different *P. aeruginosa* isolates and quantitative *P. aeruginosa* was determined by routine methods [8].

2.6. Inflammatory measures

Changes in C-reactive protein (CRP) and leukocyte count were regarded as main outcome parameter for assessment of general inflammatory status and measured before and after treatment.

2.7. Safety measures

To assess the safety of the therapeutic regimens, alkaline phosphatase (AP), serum glutamic oxaloacetic transaminase (GOT) and serum glutamic pyruvic transaminase (GPT) as liver function laboratory parameters were measured before and after therapy. Analysis was performed as comparison of mean difference between treatment groups. As additional measures of safety, the level of creatinine, full blood count and the number of recorded adverse effects, independently of their nature, were compared between treatment groups.

2.8. Statistical analysis

Analysis was performed by calculation of the mean difference between treatment groups and comparison by unpaired *t*-test taking into account unequal variances. Exact two-sided *p*-values are given for *p*-values below 0.05, which were regarded as significant. Data analyses were performed using STATA version 8.2 for Windows (STATA Corporation, College Station, TX, USA).

3. Results

127 patients were enrolled into this study in total, 64 in the CEF group, 63 in the MER group. Four and five patients respectively were excluded, as they did not fulfil the

Table 1
Summary of patient population, demographic and characteristics at baseline

	MER	CEF
Indications	59	59
(1) Suppression	36	42
(2) Exacerbation	20	14
(3) Eradication	3	3
Age (years)	17.3 (8.7)	16.9 (7.7)
Age groups (years)		
0–6	5	5
7–12	14	10
13–18	10	20
>18	30	24
Male gender	29	30
Weight (kg)	42.0 (17.4)	43.3 (18.4)
FEV1 [%-pred]	52.2 (27.1)	55.3 (24.8)
FVC [%-pred]	68.5 (24.9)	66.4 (20.6)
MEF25 [%-pred]	20.1 (19.2)	23.8 (24.7)
Ps types [number]	2.46 (1.22)	2.41 (1.37)
Ps CFUs [10^8/g sputum]	2.37 (2.73)	2.07 (2.58)

Demographic data are given in absolute numbers; characteristics data are given as mean and standard deviation in parenthesis.

inclusion criteria (five patients without any evidence of *P. aeruginosa*, two patients had also been prescribed additional oral antibiotics and in two patients the IV antibiotic therapy was changed during the trial), leaving 59 patients in each treatment group for intention to treat analysis. Details of the baseline demographics are given in Table 1, showing no differences between the treatment groups.

3.1. Efficacy

Results of efficacy measures are reported in Table 2a. Taken together, there was a significant improvement for lung function values and a significant reduction in bacterial sputum burden and systemic inflammatory status between before and after treatment for both treatment groups. For none of these efficacy measures a significant difference between treatment groups was found (Table 2a).

Results were not different for subgroup analysis according to indication as shown in detail for the subgroup of CF patients that received IV antibiotics as prophylactic suppression therapy for chronic *P. aeruginosa* infection (Table 2b).

3.2. Safety

3.2.1. Side effects

Safety data from all enrolled patients who received at least one dose of study medication demonstrated that there were a similar proportion of patients with adverse effects attributed to the medication, *i.e.* side effects in both treatment groups. Side effects occurred in 11 patients of the MER group (nausea in 2 patients; headache in 2 patients; diarrhoea in 3 patients; allergic reactions in 2 patients, in one of these this led to the withdrawal from the study; nose bleeding in one patient and fatigue in one patient) and in 10 patients of the CEF group (nausea in 3 patients, one of these had to stop the study; headache in one patient; diarrhoea in 3 patients; allergic reaction in one patient; acute pancreatitis in one patient and recurrent problems with the IV-line in another patient; both side effects leading to withdrawal from the study in these subjects).

3.2.2. Liver and renal function tests and blood count

Results of liver and renal functions tests as well as blood count are reported in Table 3. Taken together, there was no significant difference between treatment groups for any of the parameters, except for AP levels, with a decrease in the CEF group and an increase in the MER group (Table 3).

When safety measures were examined only in the subgroup of CF patients that received IV antibiotics as prophylactic suppression therapy for chronic *P. aeruginosa* infection, no differences between treatment groups were observed for any of the safety measures (data not shown).

4. Discussion

This prospective randomised clinical trial examined the efficacy and safety of intravenous antibiotic combination therapy in CF patients. Both combinations resulted in improvements of pulmonary function, bacteriological sputum burden and systemic inflammatory status. Whereas no

Table 2a
Efficacy of IV meropenem/tobramycin compared to IV ceftazidime/tobramycin in CF patients for the ITT group and all indications ($n=59$ in the MER group and 59 in the CEF group)

	MER pre [a]	MER post [a]	CEF pre [a]	CEF post [a]	Difference between treatment groups (MER-CEF) [b]
FEV1 [%-pred]	52.2 (27.1)	57.3 (26.8)	55.3 (24.8)	61.4 (25.8)	7.49 (−10.44 to +25.43)
FVC [%-pred]	68.5 (24.9)	72.4 (22.9)	66.4 (20.6)	71.2 (21.0)	1.22 (−6.54 to +8.99)
MEF25 [%-pred]	20.1 (19.2)	21.3 (20.8)	23.8 (24.7)	29.1 (27.2)	4.71 (−29.73 to +39.16)
Ps types [number]	2.46 (1.22)	1.65 (1.16)	2.41 (1.37)	1.64 (1.24)	−0.13 (−0.62 to +0.37)
Ps CFUs [10^8/g sputum]	2.37 (2.73)	1.26 (2.06)	2.07 (2.58)	0.55 (0.94)	1.09 (−0.12 to +2.30)
Leucocytes [G/l]	10.6 (3.98)	9.89 (3.12)	11.3 (5.49)	9.72 (5.48)	0.86 (−0.50 to +2.23)
CRP [mg/l]	18.8 (25.4)	12.1 (18.3)	21.4 (36.7)	11.0 (20.1)	7.01 (−4.98 to +19.01)

[a] The mean (±SD) is given for baseline values (pre) and values after therapy (post) for the respective treatment regimen.
[b] The difference of the change between MER and CEF is given as mean difference with 95%-confidence intervals in parentheses. The change in lung function parameters was calculated as percentage change from baseline. None of the differences were statistically significant (p-value derived from the t-test taking into account unequal variances <0.05).

Table 2b
Efficacy of IV meropenem/tobramycin compared to IV ceftazidime/tobramycin in CF patients of the routine suppression group only ($n=36$ in the MER group and 42 in the CEF group)

	MER pre [a]	MER post [a]	CEF pre [a]	CEF post [a]	Difference between treatment groups (MER-CEF) [b]
FEV1 [%-pred]	54.3 (22.9)	59.8 (23.9)	54.9 (25.9)	61.6 (25.4)	−0.96 (−12.29 to +10.37)
FVC [%-pred]	64.7 (19.9)	70.5 (19.5)	67.7 (22.0)	72.7 (20.7)	1.95 (−8.16 to +12.05)
MEF25 [%-pred]	25.5 (19.9)	28.6 (22.5)	20.4 (24.7)	24.8 (26.2)	−12.35 (−40.12 to +15.42)
Ps types [number]	2.44 (1.31)	1.71 (1.36)	2.37 (1.24)	1.47 (1.02)	0.07 (−0.58 to +0.73)
Ps CFUs [10^8/g Sputum]	2.67 (3.39)	0.56 (0.63)	1.82 (1.70)	1.05 (2.26)	−1.47 (−3.17 to +0.23)
Leucocytes [G/l]	10.7 (4.66)	9.21 (3.46)	11.5 (5.70)	10.23 (6.04)	−0.41 (−2.18 to +1.36)
CRP [mg/l]	14.6 (16.9)	9.7 (19.1)	23.6 (42.9)	9.98 (15.9)	8.52 (−7.08 to +24.12)

See footnotes of Table 2a for explanation.

difference between treatment groups was seen for all the efficacy outcomes, patients of the meropenem group showed a higher increase in AP values compared to patients of the ceftazidime group.

Morbidity and mortality in patients with CF is mainly due to a chronic relapsing bronchopulmonary infection caused by *P. aeruginosa* [1,9]. Therefore cystic fibrosis patients often require life-long repeated courses of intravenous antibiotic treatment for many years. Nevertheless, only very sparse data on efficacy and safety of these widely used antibiotic treatment combinations are available from CF patients, randomised trials including different treatment regimens are either not comparing antibiotic combination therapies or include only low numbers of patients [10–14]. Thus, this trial with 118 patients is one of the largest prospective studies comparing parenteral combination antibiotic therapy in CF patients. A recent report of Blumer et al. studied in a comparable design CF patients suffering from acute pulmonary exacerbations [7]. They found a significant improvement from baseline for pulmonary function and no difference between treatment groups for any of the examined lung function values. We confirm these findings in a different CF population, being of importance, as it is well known that patients from different CF populations and centers show variability *e.g.* in microbiological colonization [15] and their genetic background [16]. As two thirds of our patients were included for suppression therapy of chronic infection with *P. aeruginosa* without exacerbation of pulmonary symptoms, we expand this knowledge to a different patient group. This helps to appraise the regular prophylactic use of intravenous antibiotic therapy in general and specifically the use of meropenem in combination with tobramycin.

There are some differences between our results and the results reported by Blumer et al. They found a higher treatment response for FEV1 (relative change of 29.4 and 38.8%-predicted *versus* 13.0 and 20.4%-predicted in our study) and reported more adverse events due to elevated liver function tests [7]. Although we can only speculate, we suspect differences in patient demographics, disease state, organ involvement or concomitant therapy to be the reason for these differing results.

A decrease for AP was seen in the patients of the CEF group compared to an increase in the patients of the MER group. Blumer et al. also reported 4-times more adverse events due to AP increase in the MER group compared to the CEF group [7]. Although this might indicate a higher hepato-biliary toxicity of meropenem compared to ceftazidime, which has also been reported for CF patients by others [12], these findings have to be interpreted carefully. The source of elevated AP is not defined and may be liver, intestine or bone, especially in growing children [17]. Elevation of AP is a relatively common finding, especially in adolescence and in CF patients [18,19], and as such does not generally indicate the presence of hepato-biliary disease [20]. Irrespective of the source of the AP, during intravenous treatment with meropenem and tobramycin liver enzymes should be monitored carefully, even more carefully in CF patients with predisposition to liver damage or pre-existing liver disease.

With the results of this prospective multicenter open-label interventional study, we demonstrate that meropenem in combination with tobramycin is as useful for treatment of *P. aeruginosa* infection in cystic fibrosis patients as ceftazidime with tobramycin. In addition to its clinical efficacy, we demonstrate for the first time a direct anti-pseudomonal

Table 3
Safety of IV meropenem/tobramycin compared to IV ceftazidime/tobramycin in CF patients for the ITT group and all indications

	MER pre [a]	MER post [a]	CEF pre [a]	CEF post [a]	Difference between treatment groups (MER-CEF) [b]
AP [U/l]	278 (141)	298 (154)	272 (128)	253 (126)	60.63 (37.13 to 84.14) *
GOT [U/l]	14.2 (6.2)	17.2 (9.8)	14.3 (5.2)	15.3 (8.8)	2.37 (−0.39 to +5.13)
GPT [U/l]	17.8 (13.1)	22.8 (13.7)	18.2 (8.6)	21.9 (13.2)	1.89 (−3.36 to +7.15)
Haemoglobin [g/dl]	13.5 (1.39)	13.3 (1.25)	13.7 (1.54)	13.4 (1.66)	0.08 (−0.35 to +0.50)
Platelets [G/l]	324 (99)	293 (92)	286 (96)	261 (88)	−8.0 (−36.1 to +20.1)
Creatinine [mg/dl]	0.62 (0.20)	0.64 (0.25)	0.64 (0.23)	0.65 (0.23)	0.03 (−0.05 to +0.10)

[a] The mean (±SD) is given for baseline values (pre) and values after therapy (post) for the respective treatment regimen.

[b] The difference of the change between MER and CEF is given as mean difference with 95%-confidence intervals in parentheses.

* Indicates a statistical significant difference between groups (p-value derived from the t-test taking into account unequal variances <0.05).

effect of the MER combination *in vivo*. Although the clinical relevance of the AP increase in the meropenem group is not known yet, we suggest to use meropenem in a cautious way and to monitor liver function.

Conflict of interest

AB, DR and MG were investigators in this trial, participated in data management and writing of the manuscript and have no conflicts of interest. PL, MF and MK participated in data management, interpretation and writing of the manuscript and have no conflicts of interest.

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