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Temocillin in the treatment of *Burkholderia cepacia* infection in cystic fibrosis

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Abstract

Background: Infections due to *Burkholderia cepacia* complex (*Bcc*) strains increase morbidity and mortality in cystic fibrosis (CF). Some transplant centres reject *Bcc* infected patients. We reviewed the results in patients treated with i.v temocillin.
Methods: Twenty-three patients who received 38 courses of temocillin (1988–1998) were identified from the CF database at Royal Brompton Hospital. In three patients' data were inadequate; therefore analysis was done in 20. Outcome was measured as improvement, deterioration or no change (compared to admission) in the following categories: clinical (temperature, dyspnoea, sputum volume, chest pain), physiological (FEV1, FVC, oxygen saturation) and inflammatory markers (WBC, ESR, CRP). Patients who improved in two categories were classified as having improved. Antibiotic sensitivities and outcome were recorded.
Results: In 18 of 32 courses (56.25%) improvement occurred. The organism (*Bcc*) in eight patients' sputum became resistant (three died). The antibiotics was changed in five patients with *Bcc* strains sensitive to temocillin because of no improvement and one patient due to allergy (rash). The average time to the next i.v antibiotic was 41 days. Eight patients died (in three the *Bcc* strain was resistant to temocillin). Fourteen patients with *Bcc* were transplanted and eight patients survived. Another patient who developed *Bcc* infection post-operatively, failing to respond to temocillin.
Conclusions: These results suggest the potential benefit of i.v temocillin in CF patients with *Bcc* for exacerbations and at the time of transplantation.

Keywords: Temocillin; *Burkholderia cepacia* complex; Cystic fibrosis

1. Introduction

Burkholderia cepacia is a highly virulent organism, in certain patients with cystic fibrosis [1]. Most *B. cepacia* complex isolates are resistant to many, or all of the antibacterial agents commonly used in cystic fibrosis (CF), and selection of appropriate antibiotics for treatment of pulmonary exacerbations is therefore difficult. One report has shown that the overall proportional hazard for death is substantially enhanced if a CF patient is infected with *B. cepacia* (3.22) or *Pseudomonas aeruginosa* (2.07), compared with those infected with neither (1.00) [2].

Temocillin is a non-toxic and well tolerated antibiotic, which fails to induce β-lactamase production; it therefore does not antagonise other agents given concurrently for *P. aeruginosa* infection. In a recent study evaluating the activities of meropenem, imipenem, temocillin, piperacillin, and ceftazidime by MICs for 66 genotypically characterized *Bcc* isolates obtained from the sputum of CF patients, temocillin was one of the most active β-lactam agents [3]. Preliminary data from our unit [4] indicated that temocillin may be of benefit in the treatment of *B. cepacia* complex. This retrospective study adds a further 10 years of experience with temocillin, a β-lactamase stable antibiotic, as first and second line therapy for pulmonary exacerbations due to *Bcc* in 23 patients with CF.

Some transplant centres will not accept patients with *Bcc*. We are also able to present data detailing our experience of

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14 patients infected with *Bcc* who received transplants and were treated with temocillin post-operatively.

2. Methods

Between 1988 and 1998, a total of 38 courses of intravenous temocillin were given in combination with an intravenous aminoglycoside to 23 patients with CF (mean age 28 years, median age 25.5, range 15 to 52 years, 14 female, 9 male), for pulmonary exacerbations associated with *Bcc* complex. The mean dose was 4 g/day, (range 2–6 g/day), and the mean duration of therapy 14 days (range 1–40). A total of six courses in three patients were eliminated from the study. Five courses were eliminated because of insufficient data and in one patient the antibiotic was changed due to a rash.

The study therefore included 32 courses given to 20 patients over a ten year period.

B. cepacia complex was isolated from all pre-treatment sputum samples. The samples were cultured on plate and susceptibility was measured on disk. The Joan Stokes method was used to measure resistance. Unfortunately genotyping of these strains was not available at that time. Twelve patients were also infected with *P. aeruginosa*. One of these patients received a total of three courses, and was not infected with *P. aeruginosa* during the first course but was infected during the subsequent two courses. A patient who received three courses of temocillin also grew *P. aeruginosa* during the second and third course. One patient who received four courses cultured *P. aeruginosa* during the final course only.

Eight patients were infected with other organisms. These included *Staphylococcus aureus*, *Haemophilus influenzae*, *Aspergillus fumigatus*, and *Mycobacterium fortuitum*. Six of these eight patients were concurrently infected with *P. aeruginosa*. The case notes (medical and nursing) were reviewed, and data collected.

2.1. Outcome criteria

Outcome was measured in terms in terms of improvement, deterioration or static with no change (compared to admission baseline) in the following three categories: *clinical and physiological parameters, inflammatory markers*. This is a retrospective study and many patients were too ill at the time of admission for lung function tests and had to commence treatment before blood was taken for inflammatory markers. For these reasons data is incomplete and statistical analysis is largely inappropriate. The study is descriptive in nature. However, statistics using Wilcoxon signed rank test is given for the lung function.

2.1.1. Clinical

Clinical outcome was assessed by change (compared to admission baseline) in:

- Temperature
- Dyspnoea
- Sputum volume
- Chest pain

And defined as:

> Improvement; Improvement in at least three parameters; Static; No change in any parameter or improvement in less than three parameters; Deterioration; Deterioration in at least three parameters or insufficient data.

2.1.2. Physiological

Physiological outcome was assessed by change (compared to admission baseline) in:

- FEV_1
- FVC
- Oxygen saturation

And defined as:

> Improvement: improvement in at least two parameters; static; no change in any parameter or improvement in less than 2 parameters; deterioration; deterioration in 2 or 3 parameters.

2.1.3. Inflammatory markers

Haematological and biochemical indices were used as outcome measures and assessed by change, (compared to admission baseline) in:

- White blood cell count
- Erythrocyte sedimentation rate
- C-reactive protein

And defined as for Physiological parameters.

2.2. Overall outcome

2.2.1. Improvement

If improvement occurred in at least two categories (Clinical, Physiological or Inflammatory markers).

2.2.2. Partial response

If improvement in one category, and static in the remaining two categories.

2.2.3. Treatment failure

Static or deterioration in all categories or improvement in one category and deterioration in the remaining two.

2.2.4. Insufficient data

Designated if data was missing in two or more categories.

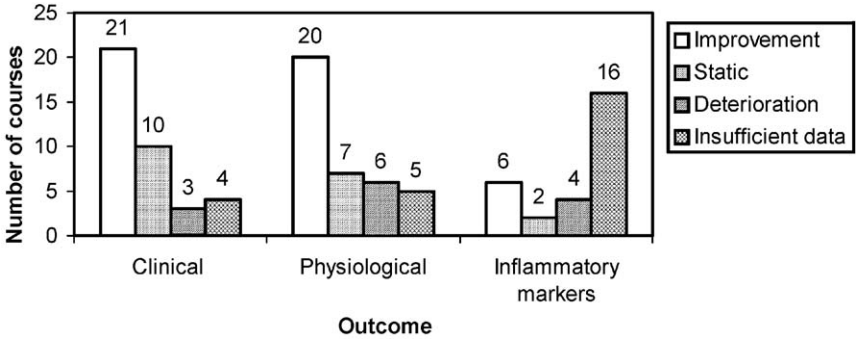

Fig. 1. Results in each category.

Sensitivities to temocillin and other antibiotics were recorded. Outcome in terms of mortality and the timing of the need of the next course of i.v antibiotics were recorded.

3. Results

Improvement occurred in 18 (56.25%) of 32 courses of temocillin given to 20 patients. A partial response was seen in two courses (6.25%) and treatment failure in 12 (37.5%).

In 21 courses significant improvement was documented in *clinical parameters* (dyspnoea, sputum volume production, and chest pain). Ten were static and three deteriorated. In four courses insufficient data was available.

In 20 courses improvement in *physiological parameters* were documented (changes in FEV_1, FVC, Oxygen saturation). In seven courses they were static and in six they deteriorated. An average improvement of 29.76% with a median of 33.3%, (range 7.7–68.75%) was documented in FEV_1. An average improvement in FVC of 29.5% with a median of 23.3% (range between 5.5% and 102%) was identified.

Paired data were available in 19 cases for FEV_1 and 18 for FVC, and the improvement was significant, 0.008 for FEV_1 and 0.0005 for FVC.

Improvement in *inflammatory markers* (WBC, ESR, and CRP) occurred in 6 courses and deterioration in 4 and 2 were static. In 16 insufficient data was available (Fig. 1).

Fourteen cases showed improvement in *clinical* and *physiological parameters*, two in a combination of *clinical*, *physiological* and *inflammatory markers,* one in *clinical* and *inflammatory markers* and one in *physiological* and *inflammatory markers*.

The indication for the use of temocillin was predominantly because of resistance to other antibiotics (24 out of 32 courses). Other reasons included failure of other antibiotics (4 out of 32 courses), and intolerance to other antibiotics (4 out of 32 courses).

Of the 18 courses given, in which the patient improved, the average timing to the next course of i.v antibiotics was 41.1 days (mean), 26.5 (median), and range 8–180 days.

Two of the patients were excluded from the study because of insufficient data, and did not require the next course of i.v antibiotics for more than 40 days indicating a positive response to temocillin. Improvement occurred after 13 courses of 22 in which the treatment had been given as first line therapy and following five courses of ten given to patients after failure of other antibiotic agents.

Eleven patients in the study received one course of i.v temocillin, four received two courses, four received three courses and one received four courses. During the first course given to each of the 20 patients, 13 patients improved, there was a partial response in one and treatment failure in six. Of the nine patients during their second course, three improved, there was a partial response in one, treatment failure in three and two were excluded because of insufficient data. Of the four patients who received three courses; one improved, there was a treatment failure in three, and one was excluded because of insufficient data. One patient who received a total of four courses, improved on three occasions, (courses 1, 2 and 4). The third course this patient received was not included in the analysis because of insufficient data (Fig. 2).

The mean interval between courses of temocillin was 29 weeks ranging from 3 to 66 weeks.

Fig. 2. Breakdown of response according to course of treatment of temocillin therapy.

3.1. Mortality data

Eight patients died during the study; in three of these the organism had become resistant during the course of the study. Three of the patients died during the first course of i.v temocillin and in two of these the bacteria were resistant to temocillin. Two died during the second course of temocillin, in one *Bcc* had become resistant to temocillin, and in another one remained sensitive to temocillin. Both had previously responded well to temocillin. The remaining three patients died during the third course of temocillin. All had previously responded well to temocillin and *Bcc* isolates in sputum remained sensitive. Five of the eight patients that died during the course of the study were concurrently infected with *P. aeruginosa*.

3.2. Transplanted patients

Fourteen patients (two of the above) with *Bcc* were transplanted, and if *Bcc* was resistant to other routine antibiotics, they were given i.v temocillin in addition to other antibiotics posttransplantation. Eight patients survived (57.1%). Two died as a direct result of *Bcc* infection and one of these had a temocillin resistant isolate from the sputum. Four died of unrelated causes, (pleural bleeding, multi-organ failure, infection and haemorrhage). In addition to the 14, another patient developed *Bcc* infection in the post-operative period, but failed to respond to i.v temocillin and died from *Bcc* septicaemia.

4. Discussion

Temocillin was given together with an aminoglycoside as is usual practice in CF care. It is therefore not possible to separate the effects of the two antibiotics which may be synergistic. It is also known that CF patients can sometimes respond to antibiotics to which their organism is resistant in the laboratory.

Improvement occurred in 18 out of 32 courses of temocillin given to 20 CF patients with acute *Bcc* pulmonary infection. Although the number of the treatments and patients is small, it seems that the clinical efficacy of temocillin is greatest on initial use, and that subsequent reduced efficacy is not directly linked to the emergence of resistance. The time to the next course of intravenous antibiotics was 41 days.

Most *Bcc* isolates are resistant to many, or all of the antibacterial agents commonly used in CF [5], making successful treatment a challenge. Unfortunately genomovar status has only recently become available. This may have been particularly relevant to the transplantation data.

This study supports previous work from our unit [4] which describes the successful use of temocillin in the treatment of CF patients with both *Bcc* and *P. aeruginosa*. In addition, we are able to present our experience of 14 patients with *Bcc*, who were transplanted. Encouragingly, eight patients survived, and only two deaths occurring as a direct result of *Bcc* infection.

This study is a review of case notes in an area where cases are few and a controlled trial was not possible. Many patients were too ill for all measurements to be taken before treatment was started. Detailed statistical analysis was therefore not appropriate.

Temocillin is a non-toxic agent and well tolerated enabling repeated courses to be given safely. Temocillin is suitable for twice daily administration enhancing acceptability and fails to induce β-lactamase production and therefore does not antagonise other agents given concurrently for concomitant *P. aeruginosa* infection [6]. Cross-resistance with other β-lactam antibiotics is rarely seen [7], and bactericidal activity in vitro is little influenced by inoculum size [7].

Patients with *Bcc* may be successfully transplanted while those with genomovar III may be more challenging [8–10]. Further controlled clinical studies comparing the use of temocillin with other agents active against *Bcc* are warranted.

These findings suggest the potential benefit from i.v temocillin in CF patients with *Bcc*, both for the treatment of exacerbations and at the time of transplantation.

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