Outcomes of Patients with Melioidosis Treated with Meropenem

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Melioidosis, an infection due to Burkholderia pseudomallei, is endemic in southeast Asia and northern Australia. We reviewed our experience with meropenem in the treatment of severe melioidosis in 63 patients over a 6-year period. Outcomes were similar to those of ceftazidime-treated patients (n = 153) despite a deliberate selection bias to more-unwell patients receiving meropenem. The mortality among meropenem-treated patients was 19%. One patient had a possible drug fever associated with the use of meropenem. We conclude that meropenem (1 g or 25 mg/kg every 8 h intravenously for ≥14 days) is an alternative to ceftazidime and imipenem in the treatment of melioidosis. The use of meropenem may be associated with improved outcomes in patients with severe sepsis associated with melioidosis.

MATERIALS AND METHODS

The Royal Darwin Hospital is a 300-bed referral center based in Darwin, Australia, and receives patients from the Top End of the Northern Territory, an area where melioidosis is endemic. Since 1989, we have prospectively documented clinical details on all cases of melioidosis seen in the Top End (5).

Melioidosis has been used in selected cases of melioidosis at our institution since August 1997. We advocate the use of meropenem at 25 mg/kg (up to 1 g) every 8 h with trimethoprim/sulfamethoxazole (8/40 mg/kg, or up to 320/1,600 mg every 12 h), with a total duration of intensive intravenous therapy of at least 14 days, followed by an extended course of oral eradication therapy. For patients with impaired renal function except patients on hemofiltration (6), the dose of meropenem was adjusted by altering both dose and interval according to established guidelines (22).

For this study, clinical details were reviewed for patients treated for melioidosis since August 1997. For this study, we defined two groups; the meropenem group comprised patients that received meropenem as part of their therapy for melioidosis (including patients switched from ceftazidime), and the ceftazidime-only group received ceftazidime as treatment and excluded patients that received carbapenems during their therapy course.

Indications for the use of meropenem included patients with critical illness (including severe sepsis) admitted to intensive care for management, clinical failure, or intolerance to ceftazidime and relapse following therapy with ceftazidime. Other patients received ceftazidime plus trimethoprim/sulfamethoxazole as initial therapy. We specifically sought details of possible adverse events, treatment failure requiring a change in therapy, and disease relapse.

At our institution, patients were referred to the intensive care unit for management of severe sepsis, respiratory failure due to poor gas exchange or poor conscious state, or renal replacement therapy for acute and/or chronic renal failure. Standard management of patients with severe sepsis, defined by standard criteria (1), including melioidosis, included the routine use of granulocyte colony-stimulating factor (since 1998) (18), early goal-directed resuscitation strategies similar to those previously published (12), early enteral feeding, the use of sedation protocols (3) (all since 1998), and physiological dose steroids (2) (since 2001).

Statistical tests were performed with Intercooled Stata 7.0 (College Station, Tex.). For comparisons of proportions, Fisher’s exact test was used. For comparisons of nonparametric distributions, the Mann-Whitney U test was used. Statistical differences were deemed significant at the 0.05 level.

Approval to review data for this study was given by the Human Research Ethics Committee of the Department of Health and the Menzies School of Health Research.

RESULTS

During the period from 1 August 1997 to 31 July 2003, 217 patients were treated for melioidosis at our institution. Mero-
penem was administered to 63 patients; 5 patients relapsed and were retreated, giving a total of 68 admissions. Among the patients treated with meropenem, 19% died (8 deaths attributable to melioidosis and 4 to unrelated causes: one each to suicide, nonmelioidosis sepsis, heart failure, and metastatic carcinomatosis).

In comparison, ceftazidime was used exclusively in 154 patients (including 11 patients readmitted due to relapse; total, 165 admissions). Among these patients, the mortality rate was 18% (16 attributable to melioidosis and 12 due to underlying disease). The characteristics of the patients are detailed in Table 1. Higher proportions of patients treated with meropenem had severe sepsis and bacteremia (P < 0.001), reflecting our selection criteria for the use of this antibiotic. In the subgroup with severe sepsis, the use of meropenem was associated with a lower mortality than ceftazidime (25% versus 76%, P < 0.001).

Of the 68 episodes where meropenem was used, the majority began on meropenem as initial therapy (n = 48). The reasons for the initial choice of meropenem were severe sepsis, including septic shock (n = 28), central nervous system infection (n = 4), relapsed disease following apparently successful treatment with ceftazidime (n = 8), and other clinical reasons (n = 8), including a single patient from whom a ceftazidime-resistant strain was isolated. In addition, ceftazidime was used initially in 20 admissions where there was a subsequent change to meropenem, 17 for worsening clinical condition on treatment and 3 for suspected adverse reactions (rash in 2 and thrombocytopenia in 1). Ceftazidime was used subsequent to the course of meropenem in 12 episodes, in 9 cases once the patient’s clinical status had stabilized, and to facilitate discharge for home therapy with continuous ceftazidime infusion via elastomeric pump. One patient was treated initially with imipenem and later changed to meropenem.

There were one probable and three possible adverse events associated with the use of meropenem. One patient had ongoing fever and neutropenia that resolved once therapy had been changed to a ceftazidime-based regimen. One patient had seizures associated with intracranial infection that occurred both prior and subsequent to the commencement of meropenem treatment. One patient had a rash while on meropenem and trimethoprim/sulfamethoxazole that resolved after the antibiotics were changed to chloramphenicol and doxycycline. One further patient had thrombocytopenia which persisted following cessation of meropenem; therapy with meropenem was later recommenced once his thrombocytopenia had resolved without incident. No patients required a change in therapy due to abnormal liver function with meropenem.

No strains that had primary resistance to meropenem were isolated. A thoracotomy and change in therapy from meropenem to ceftazidime in one patient was prompted by an increasing MIC of meropenem (0.75 to 4 mg/liter), but this strain remained sensitive.

This series included 21 patients treated with granulocyte colony-stimulating factor, 19 of whom have been reported previously (4).

**DISCUSSION**

Although meropenem has been used for the treatment of melioidosis in isolated cases (8, 9, 13), this observational study is the first to demonstrate positive outcomes in melioidosis with meropenem. Although we are not able to quantify any benefits in this observational study, the overall mortality rate that we observed is similar to that for ceftazidime-treated patients despite a deliberate selection bias toward patients with more severe infections to receive meropenem. More specifically, the mortality in those with severe sepsis was lower with meropenem.

Despite its expense, meropenem provides practical and the-
oretical advantages over both ceftazidime and imipenem. Unlike imipenem, meropenem is not associated with seizures, a particular concern for patients with renal failure and patients with intracerebral infection. In addition, meropenem has a more favorable dosing schedule (three versus four times per day) than imipenem. Compared to ceftazidime, carbapenem antibiotics have a lower MIC for a faster time-kill profile (17), including resistant isolates of Pseudomonas pseudomallei (10, 16, 23) and a faster time-kill profile (17), including resistant isolates (16). Additionally, carbapenems demonstrate a postantibiotic effect not seen with ceftazidime (19) and are associated with decreased endotoxin release (14). These factors may be important in critically unwell patients requiring more rapid control of high bacterial loads and proinflammatory dysregulation. Although a previous clinical trial in which imipenem was compared to ceftazidime failed to find any mortality benefit (15), we observed a significant reduction in mortality among patients with severe sepsis. This may reflect an interaction between other intensive-care interventions in our developing-world context and the use of meropenem.

Many other factors are likely to contribute to the low mortality observed in this study compared to those published previously (7, 11, 15), including early diagnosis and treatment, the availability of resources for intensive-care management, the use of granulocyte colony-stimulating factor, and evidence-based protocols for severely septic patients. Our evidence also supports the use of ceftazidime in milder infections and to complete the intensive phase in an outpatient setting, which is not possible with meropenem due to its poor stability.

In this study, we noted that meropenem is associated with outcomes at least as good as those obtained with ceftazidime. Theoretical considerations support our data, which suggest that its use may be associated with improved outcomes in patients with severe sepsis in a setting where other intensive-care interventions have been optimized. This hypothesis deserves further scrutiny in appropriately powered randomized controlled trials. Meanwhile, this work supports Australian guidelines listing meropenem as an alternative first-line agent in the treatment of severe melioidosis (5, 22).

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