The Efficacy of Imipenem/Cilastatin in the Treatment of Melioidosis: A Preliminary Report from Srinagarind Hospital

Paithoon Boonma, M.D.*
Watchara Boonsavat, M.D.*
Boonsong Patjanasootorn, M.D.*
Ploenchan Chetchotisakd, M.D.*
Supaporn Puapermpoonsiri, M.S.**

Abstract

A study on the effectiveness of imipenem in the treatment of melioidosis is reported. Nine of 10 enrolled patients were diagnosed melioidosis by the criteria of positive culture at site of infection and one patient by positive IHA antibody to *P. pseudomallei*. Most of them had underlying diseases as well as moderate to far advance of the disease. Nine patients showed clinical improvement with imipenem therapy, only one patient did not respond and deteriorated to septic shock and respiratory failure. The organism was eradicated in 5 patients. No serious side effect was observed. The result of this study shows that imipenem may be beneficial in treatment of melioidosis. However, a further study is required to prove its role in severe melioidosis.

INTRODUCTION

Imipenem, a new beta-lactam antibiotic is produced by *Streptomyces cattleya* in combination with cilastatin (a specific inhibitor of dehydropeptidase-I enzyme). It has been shown to have wide spectrum of antibacterial activity covering aerobic and anaerobic Gram-positive and Gram-negative bacteria for many sites of infections except central nervous system. For a group of *Pseudomonas* spp., imipenem has also been shown to inhibit several species of *P. aeruginosa*, *P. fluorescens*, *P. putida*, *P. acidovorans*, and *P. pseudomallei* but it is virtually resisted by all strains of *P. maltophilia* and many strains of *P. cepacia*.

Our interest lies in melioidosis which is endemic in South-East Asia and northern Australia. It is a difficult-to-treat disease that causes high morbidity and mortality.
especially in disseminated septicemia. The MICs of imipenem against *P. pseudomallei* is quite low (range from 0.4-0.8 mg/L) and MBC is equally to or only 2 fold greater than the MIC. We conducted this study to evaluate the effectiveness and safety of imipenem in the treatment of moderate severity of melioidosis.

**MATERIALS AND METHODS**

Adult hospitalized patients with clinically suspected of melioidosis at Srinagarind Hospital, Khon Kaen University during May 1988 to March 1989 were included in the study. In this area, melioidosis would be suspected in patients whose presentation includes 4 or more of the following symptoms and signs: male patient, age under 45 year-old, presentation of any underlying diseases as follows; diabetes mellitus (DM), chronic renal failure (CRF) or renal stone, subacute to chronic community-acquired pneumonia, evidences of multifocal infections especially in liver and spleen and in particular, the discovery of Gram-negative bacteria, bipolar staining in the clinical specimen.

Enrolled patients were diagnosed and classified as shown in Table 1. These criteria were modified from the classification of melioidosis which was set up by the Infectious Disease Association of Thailand.

All clinical history and significant laboratory profiles were recorded before and after treatment during day 3-7 and day 10-14.

A laboratorys profiles included complete blood count, urinalysis, blood urea nitrogen, creatinine, electrolytes, liver function test and clinical specimens of 3 blood culture bottles, urine and other significant body fluid were processed by standard technique available in Srinagarind Hospital. For identification of *P. pseudomallei* and serodiagnosis (using indirect hemagglutination test (IHA)) were processed in the clinical microbiology unit by using previously performed criteria. An IHA titer of 1:80 or greater or a 4 fold rising in a consequent week is considered diagnostic. The antibiotic susceptibility to imipenem, co-trimoxazole, chloramphenicol, doxycycline, kanamycin, and ceftazidime were examined by the disk diffusion technique to all isolated strains of *P. pseudomallei*.

Each patient was given the trial drug 1 gm. by intravenous infusion every 8 hr. for 7-14 days. The duration of treatment was depended on their clinical improvement such as absence of fever for at least 36 hr. or absence or improvement in the clinical signs of infection. In severe renal failure, dose adjustment was required. If any patient deteriorated during imipenem treatment, the antibiotic would be changed to the available standard regimen and all reasons for discontinuation

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Positive blood culture</th>
<th>Positive culture from other site</th>
<th>Positive serology</th>
<th>Organ involvement</th>
<th>Severity Clinical progress (hours-days)</th>
<th>Shock</th>
<th>Respiratory failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated septicemia</td>
<td>Yes</td>
<td>±</td>
<td>±</td>
<td>Multiorgan or evidence of disseminated foci in one organ.</td>
<td>Rapidly frequent</td>
<td>Most frequent</td>
<td>Common</td>
</tr>
<tr>
<td>Non-disseminated septicemia</td>
<td>Yes</td>
<td>±</td>
<td>±</td>
<td>One organ</td>
<td>Moderately frequent</td>
<td>Less frequent</td>
<td>less frequent</td>
</tr>
<tr>
<td>Localized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) simple localized</td>
<td>No</td>
<td>+</td>
<td>Usually Yes</td>
<td>One organ</td>
<td>Slow</td>
<td>Usually no</td>
<td>Usually no</td>
</tr>
<tr>
<td>(b) severe localized</td>
<td>No</td>
<td>+</td>
<td>Usually Yes</td>
<td>Multiorgan or evidence of disseminated foci in one organ.</td>
<td>Moderately frequent</td>
<td>Less frequent</td>
<td>Common</td>
</tr>
<tr>
<td>Probable</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Internal organs or not found</td>
<td>Slow</td>
<td>Less frequent</td>
<td>Usually no</td>
</tr>
</tbody>
</table>

Table 1: Clinical features, classification criteria of melioidosis
Table 2 Clinical characteristics of the patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr.)</th>
<th>Sex</th>
<th>Underlying disease</th>
<th>Clinical settings on enrollment</th>
<th>Imipenem therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Site of infection</td>
<td>Positive culture</td>
<td>Melioidosis titer</td>
</tr>
<tr>
<td>1.</td>
<td>34</td>
<td>M</td>
<td>CRF</td>
<td>Pyelonephritis</td>
<td>Urine</td>
<td>ND</td>
</tr>
<tr>
<td>2.</td>
<td>72</td>
<td>M</td>
<td></td>
<td>Cutaneous abscess</td>
<td>Pus (skin)</td>
<td>1:640</td>
</tr>
<tr>
<td>3.</td>
<td>36</td>
<td>M</td>
<td>CRF</td>
<td>Pyelonephritis</td>
<td>Blood (1/3)</td>
<td>1:10</td>
</tr>
<tr>
<td>4.</td>
<td>52</td>
<td>M</td>
<td>DM</td>
<td>Multiple lung abscesses</td>
<td>Sputum</td>
<td>1:160</td>
</tr>
<tr>
<td>5.</td>
<td>41</td>
<td>F</td>
<td>DM</td>
<td>Multiple liver and splenic abscesses and R. kidney abscess</td>
<td>Blood (3/3)</td>
<td>&gt;1:5120</td>
</tr>
<tr>
<td>6.</td>
<td>31</td>
<td>M</td>
<td>DM, Malnutrition</td>
<td>Sputum</td>
<td>–</td>
<td>1:40</td>
</tr>
<tr>
<td>7.</td>
<td>48</td>
<td>M</td>
<td>Blood dyscrasia</td>
<td>Unknown</td>
<td>–</td>
<td>a 4 fold rising from 1:160 to 1:1280 in a consequent week</td>
</tr>
<tr>
<td>8.</td>
<td>30</td>
<td>M</td>
<td>Beta-Thalassemia</td>
<td>Multiple liver and splenic abscesses</td>
<td>Pus (liver)</td>
<td>1:160</td>
</tr>
<tr>
<td>9.</td>
<td>46</td>
<td>M</td>
<td>L. ureteric stone</td>
<td>Single lung abscess</td>
<td>Sputum</td>
<td>1:20</td>
</tr>
<tr>
<td>10.</td>
<td>61</td>
<td>M</td>
<td>DM, CRF</td>
<td>Chronic ulcer at L. chest wall and splenic abscess</td>
<td>Pus (skin)</td>
<td>1:2560</td>
</tr>
</tbody>
</table>

Note: R = right, L = left, ND = no data available, DM = diabetes mellitus, CRF = chronic renal failure
of imipenem were recorded.

The criteria for patient exclusion were non-melioidosis by the above criteria: patient in shock or respiratory failure before enrollment and patient with known allergy to beta-lactam antibiotics.

RESULTS

Ten out of 13 patients were finally documented for melioidosis. The remaining were sepsis of unknown causes (2) and leptospirosis(1). Table 2 showed clinical characteristics of the 10 patients. They were 9 males and one female. Mean age was 45.1 years, range from 30 to 72. Seven patients were classified as localized group (severe localized and simple localized infection in six and one patient respectively). The other 3 patients were each classified for disseminated sepsisemia, non-disseminated sepsisemia and probable group.

All except one had underlying diseases and most of them had DM or renal diseases. Patient no. 1, no. 3 and no. 10 with renal failure had uremic symptoms before enrollment which required peritoneal dialysis. Their initial blood creatinine were 15.6 mg%, 26 mg% and 27.5 mg% respectively. Three patients were diagnosed and treated as melioidosis before enrollment. All of them still had symptoms and signs of disease and positive culture when the trial drug began (patient no. 5 had three positive blood cultures, no. 6 and no. 9 had positive sputum cultures).

Most patients were treated for 7 to 14 days except no. 6, who was treated before with Augmentin (amoxycillin + clavulanic acid) but no clinical improvement was seen. His chest radiograph showed multiple abscesses of both lungs and the organism was presented in sputum smear and culture. The pneumonitis rapidly progressed and turned to adult respiratory distress syndrome (ARDS), septic shock and profound hypoglycemia after the trial drug was treated for 48 hr. Therefore the antibiotic was changed to ceftazidime and co-trimoxazole. The patient expired eventually 10 days later with the complications of ARDS; pneumothorax, intractable hypoxia and severe acidosis.

Nine patients had clinical improvements with imipenem.

The mean duration of therapy was 10.3 days. The bacteria was eradicated in 5 patients and persisted in 2 patients.

No serious side effect was observed during treatment. Only one patient (no. 7) developed a minor skin rash on the 10th day and the rash was subsided after the medication was stopped.

Antibiotic susceptibility of the isolated strains of *P. pseudomallei* was shown in Table 3.

### DISCUSSION

Antibiotics to which *P. pseudomallei* are known susceptible including chloramphenicol, co-trimoxazole, doxycycline, kanamycin and tetracycline. These “conventional drugs” have MIC$_{90}$ value against the organism within therapeutic range that varied from 3-12 mg/L. Their effectiveness for melioidosis was recently reviewed by Leelarasamee and Aswapokee. Data obtained from 285 septicemic patients revealed the better chance of survival in treated group than those who didn't but mortality was still too high to accept. (Those who received mono or combined conventional treatment had 83% fatality rate while in non-treated patient 100% died). For localized infection, there was only 2.5% mortality rate and the drugs appeared useful for long-term oral administration.

Poor prognostic factors that may affect the outcome are as follows: patient who is admitted during rainy season, presenting with shock and azotemia and the inappropriate initial antibiotic treatment. The former factors are hardly to be corrected besides for the antibiotic factor.

Nowadays, many kinds of newer beta-lactam antibiotics were reported to be more active against the organism. They are ceftazidime, piperacillin, azlocillin, mezlocillin, carumonam, and imipenem. Most of their MIC$_{90}$ levels against *P. pseudomallei* are not above 2 mg/L. Among these newer drugs, only ceftazidime had been advocated for treatment of septicemic melioidosis. The results from Khon Kaen study revealed ceftazidime plus co-trimoxazole were significantly more effective than the conventional 3 drugs regimen which include chloramphenicol, co-trimoxazole and doxycycline in reducing the mortality rate of disseminated septicemic melioidosis (82% mortality rate of the conventional drugs VS 38.4% mortality rate in ceftazidime plus co-trimoxazole; P value = 0.018).

Our report here was the first clinical study on imipenem therapy in melioidosis. Most patients were suffering from their underlying diseases and moderate to far advance of melioidosis. We found significant clinical improvement in 9 patients and the bacteria could be eradicated in 5 of 7 positive cultures.

Imipenem as a monotherapy appeared to be more effective than those conventional drugs. Two patients failed to
respond to conventional drugs even they had been treated for 7-10 days. No isolated strains of *P. pseudomallei* were resistant to imipenem. The antibiotic was well tolerated and caused no serious adverse effect.

The overall results of this study were promising for imipenem in the treatment of melioidosis. However, its benefit in severe septicemic melioidosis remains unknown and a further study is required.

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REFERENCES


