International Journal of Infectious Diseases (2007) 11, 402—406

http://intl.elsevierhealth.com/journals/ijid

Efficacy and safety of colistin (colistimethate sodium) for therapy of infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in Siriraj Hospital, Bangkok, Thailand

Pornpan Koomanachai [a], Surapee Tiengrim [a], Pattarachai Kiratisin [b], Visanu Thamlikitkul [a,*]

[a] *Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Siriraj Hospital, Mahidol University, Prannok Road, Bangkok, Thailand*
[b] *Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Received 22 June 2006; received in revised form 31 August 2006; accepted 18 September 2006
Corresponding Editor: Andy I.M. Hoepelman, Utrecht, The Netherlands

KEYWORDS
Colistin;
Pseudomonas aeruginosa;
Acinetobacter baumannii

Summary
Objective: To determine the efficacy and safety of colistin (colistimethate sodium) produced by a local pharmaceutical company in Thailand for the treatment of infections caused by multidrug-resistant (MDR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.
Methods: Patients hospitalized at Siriraj Hospital between January 2005 and April 2006, who had infections caused by MDR *P. aeruginosa* or *A. baumannii*, were enrolled in the study. Colistin (colistimethate sodium) at a dosage of 5 mg/kg/day was given intravenously in two divided doses. Primary outcomes were the clinical response and 30-day mortality; secondary outcomes were microbiological response and adverse events.
Results: Ninety-three patients infected with MDR *P. aeruginosa* and *A. baumannii* were enrolled. Seventy-eight patients (71 with *A. baumannii* and seven with *P. aeruginosa*) received colistin, whereas 15 patients (12 with *A. baumannii* and three with *P. aeruginosa*) received other antibiotics. The mean age, gender, underlying conditions and severity of illness of the patients in both groups were not significantly different. In the colistin group, 63 patients (80.8%) had a favorable clinical response and 94.9% had a microbiological response. The overall mortality of the patients in the colistin group was 46.2% and that in the non-colistin group was 80%. Nephrotoxicity was found in 24 patients (30.8%) in the colistin group and 17 of them had predisposing factors contributing to their renal dysfunction. No neurotoxicity was observed among the 78 patients.

* Corresponding author. Tel.: +66 2 412 5594; fax: +66 2 412 5994.
E-mail address: visanut@yahoo.com (V. Thamlikitkul).

doi:10.1016/j.ijid.2006.09.011

Conclusion: Locally produced colistin appears to be safe and effective for the treatment of infections caused by MDR *P. aeruginosa* and *A. baumannii* in Thai adult patients.

Introduction

Nosocomial infections caused by multidrug-resistant (MDR) organisms are emerging worldwide.[1–3] The incidence of MDR pathogens, particularly *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, in Thailand has dramatically increased.[4] A prospective cohort study of 208 clinical isolates of *A. baumannii* recovered from the patients in Siriraj Hospital from January to December 2002, revealed that 86 strains (41.3%) were isolated from the infected patients and the remaining 58.7% were colonizers.[5] In this study, 57% of *A. baumannii* isolates were resistant to all antimicrobial agents available in Thailand including beta-lactams, aminoglycosides and fluoroquinolones, and the overall mortality rate of the patients infected with pandrug-resistant *A. baumannii* was 79%.[5] The study of 104 clinical isolates of *A. baumannii* from 100 hospitalized patients at Maharaj Nakorn Chiang Mai hospital, Thailand also observed that 46% of the isolates were pandrug-resistant and the overall mortality was 52%.[6]

Over the past few years there have been reports on treating patients infected with MDR *A. baumannii* and *P. aeruginosa* with polymyxin B and colistin.[7–9] They found that polymyxin B and colistin had modest efficacy and were safe. In vitro activity of polymyxin B and colistin against 100 clinical isolates of MDR *A. baumannii* and 100 isolates of *P. aeruginosa* collected from the patients hospitalized at Siriraj Hospital from 2002 and 2003, revealed that all isolates were susceptible to polymyxin B and colistin.[10] However polymyxins are not available in Thailand and international pharmaceutical companies do not have a policy to import polymyxins to Thailand. Therefore we asked a local pharmaceutical company to produce colistin and this product has been approved by the Thai Food and Drug Administration since 2004.

The objective of this study was to determine the efficacy and safety of colistin produced by a local pharmaceutical company in Thailand for the treatment of infections caused by MDR *P. aeruginosa* and *A. baumannii*.

Methods

The study was approved by the ethics committee on human research of the Faculty of Medicine Siriraj Hospital, and all participating subjects signed the informed consent form. This was a pragmatic clinical trial conducted at Siriraj Hospital, Bangkok, Thailand, between January 2005 and April 2006. The eligible subjects were hospitalized patients over the age of 18 years who were infected with *A. baumannii* or *P. aeruginosa* resistant to beta-lactams, fluoroquinolones and aminoglycosides. We excluded patients with infections caused by *A. baumannii* or *P. aeruginosa* with other bacteria from our study because we felt that it was difficult to determine the efficacy of colistin for treatment of infections caused by MDR *A. baumannii* or *P. aeruginosa*. Colistin was offered to all such patients and if the patients and their responsible physicians agreed to have colistin treatment, the patients received intravenous colistin (colistimethate sodium) of 5 mg/kg/day in two divided doses. The dosage of colistin was adjusted according to the patients' renal function.[11] If the patients or their responsible physicians did not wish to join the study, they received other antibiotics according to their physicians' decisions and these patients were defined as the 'non-colistin group'.

All isolates of *A. baumannii* and *P. aeruginosa* from the eligible patients were tested for colistin susceptibility by E-test according to the manufacturer's guidelines (AB Biodisk, Sweden). A suspension of each isolate in Mueller–Hinton broth (BBL-Becton Dickinson, USA), adjusted to the density of a 0.5 McFarland standard, was swabbed in three directions to ensure uniform growth onto Mueller–Hinton agar (BBL-Becton Dickinson, USA) plates. Once the agar surface was completely dry, an E-test colistin strip (ranging from 0.06 to 1024 μg/ml) was applied to each plate and the plates were incubated at 35 °C for 16–20 hours. The minimum inhibitory concentration (MIC) was read where inhibition of growth intersected the E-test strip. Quality control strains of *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were used with the reference MIC range of 0.125–0.5 and 0.5–2 mg/l, respectively. The susceptible isolate was defined as having a MIC of $\leq$2 mg/l. Quantitative colistin serum level was determined by microbiological assay.[12]

The primary outcomes were the clinical response and 30-day mortality. A good clinical response referred to a combination of clinical cure and clinical improvement. Clinical cure was defined as a disappearance of symptoms and signs of infection and clinical improvement was defined as a partial resolution of the symptoms and signs of infection. The secondary outcomes were microbiological response and adverse effects. Successful microbiological response was defined as an eradication of the causative organisms at the end of treatment. Nephrotoxicity was defined as an increase in serum creatinine of at least two-fold of the baseline value or a 30% decrease of creatinine clearance from the baseline value.

Results

Between January 2005 and April 2006, 93 patients met the inclusion criteria. Seventy-eight patients were in the colistin group and 15 patients in the non-colistin group. The baseline characteristics of the patients are shown in Table 1. The mean age, gender, underlying conditions, and severity of illness of the patients in both groups were not significantly different.

Presenting infections in the colistin group were: pneumonia (54), bacteremia and/or catheter related infection (9), intra-abdominal infection (5), urinary tract infection (4), skin and soft tissue infection (5), and sinusitis (1). In the colistin group, 71 patients (91%) were infected with *A. baumannii* and

Table 1 Baseline characteristics of the patients

Characteristic	Colistin group (*N* = 78)	Non-colistin group (*N* = 15)
Male	45 (57.7%)	11 (73.3%)
Mean age, years (range)	63.5 (18—103)	58.9 (27—90)
ICU admission	45 (57.7%)	5 (33.3%)
Mechanical ventilation	62 (79.5%)	14 (93.3%)
Mean APACHE II score	21.9	22.3
Pre-existing renal impairment (serum creatinine ≥1.5 mg/dl)	37.2%	40%
Pathogenic organism		
Acinetobacter baumannii	71 (91.0%)	12 (80%)
Pseudomonas aeruginosa	7 (9.0%)	3 (20%)
Underlying condition		
Diabetes mellitus with or without other medical conditions	16 (20.5%)	1 (6.7%)
Cardiovascular diseases	3 (3.9%)	3 (20%)
Cancers	6 (7.7%)	1 (6.7%)
Immunosuppressive treatment	4 (5.1%)	—
Cerebrovascular diseases	7 (9.0%)	—
Chronic obstructive pulmonary disease	7 (9.0%)	—
Other chronic medical conditions	12 (15.4%)	4 (26.7%)
Traumatic surgical patients	10 (12.8%)	4 (26.7%)
Recent cardiovascular surgery	8 (10.3%)	2 (13.3%)
Recent brain surgery	4 (5.1%)	—
Recent abdominal surgery	1 (1.3%)	—

seven (9%) were infected with *P. aeruginosa*, whereas 12 patients (80%) were infected with *A. baumannii* and three (20%) were infected with *P. aeruginosa* in the non-colistin group. In vitro susceptibility tests determined by E-test revealed that all *A. baumannii* and *P. aeruginosa* isolates had a MIC of colistin less than 2 mg/l and were considered susceptible to colistin. In the colistin group, 33 patients (42.3%) received colistin alone, whereas 45 patients (57.7%) received colistin with other antibiotics including vancomycin, aminoglycosides, metronidazole or carbapenems. In the non-colistin group, the patients received carbapenems (6), cefoperazone/sulbactam (3), cefoperazone/sulbactam combined with netilmicin (4), and cefoperazone/sulbactam combined with carbapenem (2).

The treatment outcomes are shown in Table 2. Sixty-four patients (82.1%) in the colistin group had a good clinical response. The clinical response in the patients who received colistin alone was 84.8% and in those who received colistin with other antibiotics was 77.8%; only four patients (26.7%) in the non-colistin group responded.

All cause mortality within 30 days was 46.2% in the colistin group and 80% in the non-colistin group ($p = 0.03$). The relative risk of death in the colistin group was 0.58 of the non-colistin group with a 95% confidence interval (CI) of 0.41 to 0.82. The difference in mortality was statistically significant and the number needed to treat (NNT) was approximately three, which implies that only three patients infected with MDR *A. baumannii* or *P. aeruginosa* needed to be treated with colistin in order to prevent one additional death. The overall mortality rates of the patients infected with *A. baumannii* and *P. aeruginosa* in the colistin group were 46.5% and 42.9%, respectively.

A microbiological response was found in 94.9% of the patients in the colistin group and none in the non-colistin group. Nephrotoxicity was observed in 24 patients (30.8%) in the colistin group. The incidence of nephrotoxicity of the patients in the colistin group was significantly less than that in the non-colistin group. Seventeen (70.8%) of 24 patients in the colistin group who developed nephrotoxicity had other predisposing factors contributing to a decline in renal function including nephrotoxic drugs, chronic kidney diseases, and hypovolemia. Nephrotoxic effects were mild and reversible without requiring renal replacement therapy. No neurotoxicity or drug reaction was observed in the patients who received colistin. The average dose of colistin was 179.6 mg/day, the average duration of colistin treatment was 11.9 days, and the average total dose of colistin was 2.1 g/patient/course.

Table 2 Treatment outcomes of the patients

Outcome	Colistin group (*N* = 78)	Non-colistin group (*N* = 15)	*p* Value
Good clinical response	63 (80.8%)	4 (26.7%)	<0.001
All cause mortality within 30 days	36 (46.2%)	12 (80%)	0.03
Microbiological response	74 (94.9%)	0	<0.001
Nephrotoxicity	24 (30.8%)	10 (66.7%)	0.02
Neurotoxicity	0	0	

Discussion

This study used colistimethate sodium (also called colistin methanesulfate, pentasodium colistimethane sulfate, or colistin sulfonyl methate), which is less potent and less toxic than colistin sulfate.[13,14] Colistin has a narrow spectrum of antimicrobial activity and is active against most aerobic Gram-negative bacilli including *P. aeruginosa* and *Acinetobacter spp*, even the organisms that are multidrug-resistant.[13] Several reports published during the period 1999 to 2003 revealed that polymyxins were effective and safe for treatment of patients infected with MDR Gram-negative bacteria including *A. baumannii* and *P. aeruginosa*.[7–9] We therefore attempted to study the efficacy and safety of locally produced colistin.

We were unable to do a randomized controlled study to compare colistin with other antibiotics since it would be unethical to provide antibiotics likely to be ineffective to patients, while the antibiotic active against the causative pathogens, colistin, was available. Therefore we had to offer colistin to all patients who had infections caused by *A. baumannii* or *P. aeruginosa* resistant to beta-lactams, fluoroquinolones and aminoglycosides. However, the baseline characteristics of the patients including mean age, gender, underlying conditions, severity of illness and the sites of infections of the patients in both groups were comparable.

The results from our study also showed a good clinical outcome and less overall mortality in patients who received colistin for treatment of MDR *A. baumannii* and *P. aeruginosa*. A good clinical outcome was found in 82.1% of patients treated with colistin no matter how the patients received it, alone or with other antibiotics. Overall mortality decreased from 79% in a previous study of *A. baumannii* infections in the same hospital to 46.5% of the patients infected with *A. baumannii* treated with colistin in this study.[5] The overall mortality in the non-colistin group in this study was still up to 80%. Furthermore, NNT for mortality from our study was only three, indicating that only three patients infected with MDR *A. baumannii* or *P. aeruginosa* needed to be treated with colistin in order to prevent one additional death. Moreover the cost of colistin was approximately 10 to 20 times lower than that of other antibiotics used to treat MDR *A. baumannii* and *P. aeruginosa* such as carbapenems, cefoperazone/sulbactam, and cephalosporins with or without aminoglycosides.

A microbiological response was observed in 74 patients (94.9%) in the colistin group. Three patients who did not have a microbiological response also had a good clinical outcome. However, antibiotic susceptibility profiles of these persistent isolates were different from those of the original isolates and these isolates could be new colonizers. In four patients who had no microbiological response after 72 hours of colistin treatment, the serum levels of colistin were measured by bioassay and the results showed that colistin levels were adequate at 4—8 times above the MIC of the organism. Therefore the same dose of colistin was continued for 7 days and all patients eventually had a microbiological response. We excluded patients with infections caused by *A. baumannii* or *P. aeruginosa* with other bacteria from our study, therefore the efficacy of colistin for treatment of mixed infections is unknown.

Nephrotoxicity is an important side effect of colistin. In our study, nephrotoxicity was found in 30.8% of the patients receiving colistin; this is comparable to the results found in a previous report.[15] Some patients in the colistin group who developed nephrotoxicity also had other contributing factors. Nephrotoxicity in these patients was mild and reversible without requiring renal replacement therapy. Some patients had improvement in their renal function after colistin treatment, which implies that the worsening of renal function was probably due to a severe infection or other conditions. The incidence of nephrotoxicity of the patients in the non-colistin group was significantly more than that in the colistin group. This observation might be due to uncontrolled infections and the side effects of medications including antibiotics given to the patients. No neurotoxicity or drug reaction was observed in the patients in our series.

Although the ability of Gram-negative bacteria to develop resistance to colistin is rare, such Gram-negative bacteria can develop resistance to colistin through mutation or adaptation mechanisms.[13,16] We therefore recommend that colistin, as the only currently available drug for the treatment of MDR Gram-negative bacteria in Thailand, should be reserved for treatment of infections caused by multidrug-resistant Gram-negative bacteria that are only susceptible to colistin.

In summary, we found that colistin appears to be safe and effective for treatment of infections caused by multidrug-resistant *P. aeruginosa* and *A. baumannii* in Thai adult patients. Treatment with colistin decreases patient mortality and is cost-effective.

Acknowledgements

The authors thank the Thailand Research Fund for supporting the study, Atlantic Pharmaceutical Co. Ltd for supplying colistin and colistin E-test strips, Ms Pornsiri Chinsawangwatanakul and Ms Sunee Thanakhumtorn for coordinating the study, and Dr Methee Chayakulkeeree for reviewing the manuscript.

Conflict of interest: No conflict of interest to declare.

References

1. Bergogne-Berezin E, Towner KJ. *Acinetobacter spp*. as nosocomial pathogens: microbiological, clinical, and epidemiological features. *Clin Microbiol Rev* 1996;**9**:148—65.
2. Livermore D. Multiple mechanisms of antimicrobial resistance in Pseudomonas aeruginosa: our worst nightmare? *Clin Infect Dis* 2002;**34**:634—40.
3. Hamberger H, Diekema D, Fluit A. Surveillance of antibiotic resistance in European ICUs. *J Hosp Infect* 2001;**48**:161—76.
4. Thamlikitkul V, Jintanothaitavorn D, Sathimethakul R, Vaiyhayaphichet S, Trakulsomboon S, Danchaivijitr S. Bacterial infections in hospitalized patients in Thailand in 1997 and 2000. *J Med Assoc Thai* 2001;**84**:666—73.
5. Keerasuntonpong A, Samakeepanich C, Tribuddharat C. Epidemiology of *Acinetobacter baumannii* infections in Siriraj Hospital. *Siriraj Med J* 2006;**58**:951—4.
6. Chaiwarith R, Mahatthanaphak S, Boonchoo M, Supparatpinyo K, Sirisanthana T. Pandrug-resistant *Acinetobacter baumannii* at Maharaj Nakorn Chiang Mai Hospital. *J Infect Dis Antimicrob Agents* 2005;**22**:1—8.

7. Markou N, Apostolakos H, Koumoudiou C, Athanasiou M, Koutsoukou A, Alamanos I, et al. Intravenous colistin in the treatment of sepsis from multiresistant Gram-negative bacilli in critically ill patients. *Crit Care* 2003;**7**:78—83.
8. Ouderkirk JP, Nord JA, Turett GS, Kislak JW. Polymyxin B nephrotoxicity and efficacy against nosocomial infections caused by multiresistant Gram-negative bacteria. *Antimicrob Agents Chemother* 2003;**47**:2659—62.
9. Levin AS, Barone AA, Penco J, Santos MI, Marinho IS, Arruda EAG, et al. Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Clin Infect Dis* 1999;**28**:2008—11.
10. Tribuddharat C, Tiensasiton C, Techachaiwiwat W, Rugdeekha S, Dhiraputtra C, Thamlikitkul V. In vitro activity of polymyxin E against multi-drug resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *J Infect Dis Antimicrob Agents* 2003;**20**:135—7.
11. Evans ME, Feola DJ, Rapp RP. Polymyxin B sulfate and colistin: old antibiotics for emerging multiresistant Gram-negative bacteria. *Ann Pharmacother* 1999;**33**:960—7.
12. Wootton M, Holt HA, MacGowan AP. Development of a novel assay method for colistin sulphomethate. *Clin Microbiol Infect* 2005;**11**:243—4.
13. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant Gram-negative bacterial infections. *Clin Infect Dis* 2005;**40**:1333—41.
14. Kaye D. Current use for old antibacterial agent. *Inf Dis Clin N Am* 2004;**18**:669—73.
15. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Crit Care* 2006;**10**:R27.
16. Moore RA, Chan L, Hancock RE. Evidence for two distinct mechanisms of resistance to polymyxin B in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 1984;**26**:539—45.