AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Meronem
ACTIVE INGREDIENT: Meropenem

Study No: SRP-HB-MER-2005/1
Antibiotic therapy for hospital-acquired infections in ICU patients. A prospective, observational, multicenter study (ANTHICUS)

Developmental phase: Post Marketing study
Study Completion Date: 12 December 2007
Date of Report: 31 December 2008

OBJECTIVES:

Primary
The primary objective of this observational study was to get a better knowledge of the patterns of use of antibiotics, with special regard to the broad-spectrum antibiotics, in ICU-patients with hospital-acquired infections, and also to evaluate possible association with a specific treatment and a type of infection and/or the patient's profile.
Secondary
Secondary objectives of the study was, in the setting of empirical treatment, to evaluate:

- the frequency of appropriate antibiotic therapy (defined as the use of antibiotic(s) with "in vitro" efficacy against the identified pathogens responsible for the infection)
- the frequency of "the strategy of de-escalation" according to the culture results

METHODS:

The patients were recruited from intensive care units and each patient was followed until discharge from the ICU, or until withdrawal of antibiotherapy (when in the ICU), or until death (when in the ICU). On the first day the patient's history of previous hospitalization in the last 4 months and antibiotic therapy in the last 1 month was documented as well as co-morbidities, type of current infection and initial antibiotic treatment. The Apache score (Acute Physiology and Chronic Health Evaluation II) was documented if available.
Throughout the observation period any changes to the therapy, with the reason for change, and the results of the bacterial sampling if available, were documented.

RESULTS:

SUMMARY OF RESULTS

The observed population consisted of 107 males and 64 females with an age range of 19 to 89 years. 81% of the population had comorbidites of which the most frequent were respiratory disease in 38.6% of the patients, cardiac disease in 34.5%, recent trauma or surgery in 22.8% and diabetes mellitus in 21.1% of patients.

In the 4 months before admission to the ICU 30.4% of patients had been hospitalized; the most frequent admission was to an internal medicine ward (39.7% of admissions) where the patients stayed a mean of 14.4 days. 6.4% of patients had been previously admitted to an ICU, the mean stay here was 15.1 days.

During the month before admission to the ICU 28.7% of all patients had received in total 21 different antibiotics. The most frequent drugs administered were the broad spectrum antibiotics amoxicillin + clavulanic acid in 9.4% of patients and piperacillin + tazobactam in 6.4% of patients.

50.9% of the patients were admitted directly into the ICU. The maximum length of stay in another ward before admission to the ICU was 164 days on an internal medicine ward and 101 days in another ICU.

66.7% of patients developed their infection on the ICU ward. The mean length of stay in the ICU before initiation of antibiotic treatment was 3.8 days (SD ±6.4).

The mean Apache score was 19.2 (±9.3) in 85 patients measured at admission to hospital, the mean score was 20.4 (±8.0) in 125 patients at ICU admission and patients 21.0 (±8.5) at start of infection in 114 patients. No conclusion can be made about the predictability of the Apache score since no information is available about patient follow up.

The most frequent infections reported were VAP (ventilation associated pneumonia) in 39.8% of patients and HAP (hospital acquired pneumonia) in 38.0% of patients. Bacteremia associated with urosepsis was reported in 7.0% of patients, bacteremia from another cause in 11.1% of patients and 8.2% of patients had peritonitis.

Antibiotics were started empirically in 138 patients (80.7%); antibiotics were given after the results of the bacterial analysis in 30 patients (17.5%) and in 2 patients the choice of antibiotic was made both empirically and based on bacteriological the results. The main motivation for the choice of the initial therapy were standard empirical treatment in the hospital for the pathology treated in 50.3% of patients and patient’s co-morbidities and/or history in 36.8% of patients.

Treatment was started with monotherapy in 52.6% of patients (n=90). The most frequent monotherapy was meropenem, which was administered to 11.1% of patients. Two combination drugs were classified as monotherapy although technically these were combination therapies. A combination of the broad spectrum amoxicillin combined with the ß-lactamase-inhibitor clavulanic acid was administered to 16.4% of patients and the combination piperacillin and tazobactam was administered to 7.0% of patients. The combination Amoxicillin + clavulanic acid was also the antibiotic given most often to the patients in the month before admission to the ICU.

The most frequent initial combination therapy was a combination of amikacin plus piperacillin and tazobactam administered to 5.3% of patients. The most frequent drug

administered within the combination therapy regime was amikacin, which was administered to 24.6% of all patients followed by meropenem administered to 10.5% of all patients.
The most frequent infections diagnosed were VAP (39.8% patients) and HAP (38.0% patients). Both HAP and VAP were treated most frequently with amoxicillin + clavulanic acid. (n=17 HAP patients ; n=19 VAP patients) and amikacin (n=14 HAP patients; n=19 VAP patients).
“Other” bacteremia was diagnosed in 11.1% patients and treated most frequently with amikacin (n= 8 patients) and meropenem (n=5 patients). Peritonitis was diagnosed in 8.2% of patients and 50% of these patients were treated with meropenem (n=7 patients).
Urosepsis occurred in 12 patients and was treated with meropenem (n=4 patients), amikacin (n=3 patients) and temocillin (n=2 patients).
The physician reported that there was no change to the initial treatment in 33.9% of patients (n=58 patients); in 56.7% of patients (n=97) the initial treatment was stopped and in 9.4% (n=16) the initial treatment was modified. Subsequent treatment was reported for 62% of patients (n=106) and in 89 patients the antibiotic was switched. Meropenem was the most frequent antibiotic administered in the subsequent therapy and the most frequent change in the subsequent therapy was to meropenem. There was a switch to meropenem in 57.3% of patients who received subsequent treatment and meropenem was added to the therapy in a further 4 patients. A switch to piperacillin + tazobactam was made in 16.9% of patients and to amikacin in 15.7% of patients.
The mean duration of initial antibiotic treatment was 8.7 (± 5.3) days for monotherapy and 7.4 days for initial combination therapy, the mean duration for subsequent therapy was 10 days (± 8.7) and 19 patients received the same treatment for more than 20 days.
Bacteriological sampling was performed in 157 patients. 16.6% of the samples were blood samples, 15.7% were bronchoalveolar lavage samples, 9.4% were urine samples and 1.8% wound samples were taken. For 63.2% of samples “other” was recorded. Under the term “other” samples from sputum, tracheal aspiration, peritoneal fluid and cerebrospinal fluid were documented.
The most common bacteria detected at least once in patients with available microbiological data was Pseudomonas aeruginosa (n=32 patients) followed by Escherichia coli in n=27 patients and Staphylococcus aureus in n=22 patients.
Testing of the gram-negative bacteria “in vitro” revealed that Pseudomonas aeruginosa showed resistance in more than one sample to 14 antibiotics, Escherichia coli showed resistance to 13 antibiotics tested “in vitro” and Enterobacter aerogene showed resistance to 10 antibiotics tested “in vitro”.
Testing of the gram-positive bacteria “in vitro” revealed that both Staphylococcus aureus and Staphylococcus coagulase-neg showed resistance in more than one sample to 10 antibiotics and Klebsiellae pneumoniae showed resistance to 9 antibiotics tested “in vitro”. Further bacteriological testing revealed that the ESBL test was positive in 29% of the 79 samples tested of these were positive for ESBL enzymes.