

MARKET RESEARCH ON USAGE OF ANTIBIOTICS IN SERIOUS INFECTIONS

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Received: 31 May 2014 Revised and Accepted: 12 Jul 2014

ABSTRACT

Objective: The main objective of the study is to prognosticate the market research on usage of antibiotics in serious infections and corresponding with the clinicians based on the preference order of drugs.

Methods: A prospective observational study was conducted for a period of six months in various hospitals in Andhra Pradesh. Analysis on Piperacillin + Tazobactam, Cefepime and Meropenem drugs used for resistant isolates were identified to be the most effective antibacterial agents. Respondents reviewed three drugs based on the dosage, duration, type of case and any specific conditions to avoid these drugs.

Results: Out of total Sample size (N=128) when assessed Piperacillin+Tazobactam (84.38%), Cefepime (12.50%), Meropenem (3.12%). The most prevalent type of case and usage of doctors to treat UTI (25.00%), Sepsis (17.86%), Severe Sepsis (14.29%), CRTI, LRTI (8.33%) and others (34.52%) were reported.

Conclusion: Piperacillin+Tazobactam is used as Ist line, Cefepime as IInd line followed by Meropenem as IIIrd line drug. When a competitor enters the market they should consider the availability of the products (domestic & generic) as per the cost effectiveness reliable to the patients which has lesser side effects, antibiotic resistance and ease for intake to the patients as per the demographical conditions is observed.

Keywords: N- respondents (doctors), UTI, CRTI, LRTI, Sepsis, Antibiotic Resistance and Competitor.

INTRODUCTION

Literature review

Antibiotics are the medications used to treat and in some cases prevent bacterial infections. According to the CDC [1] (Centers for Disease Control and Prevention), outpatient antibiotic overuse in the USA is a particular problem in the South-East. The antibiotic resistance continues to be a serious public health threat worldwide, according to the ECDC (European Centre for Disease Prevention and Control). In a statement issued in 19th November 2013, the ECDC informed that an estimated 25,000 people die each year in the European Union from antibiotic-resistant bacterial infections. New ECDC data has shown that there has been a considerable increase over the last four years of combined resistance to multiple antibiotics in *E. coli* and *Klebsiella pneumoniae* in over one third of EU and EEA (European Economic Area) nations. Consumption of carbapenems, a major class of last-line antibiotics, increased significantly from 2010 to 2013 [1].

Drug profile

Meropenem

It belongs to the class carbapenem [2]. Parent antibiotic *Thienamycin* derived from *Streptomyces cattleya* act by inhibiting cell wall synthesis which is active against both gram positive and gram negative bacteria. They are not active against methicillin-resistant staphylococci (MRSA), Enterococcus bacteria. Readily penetrates the cell wall of most gram positive bacteria and gram negative bacteria to reach PBP 2, 3 & 4 of *E. coli* and *Pseudomonas aeruginosa*, PBP 1, 2 & 4 of *Staphylococcus aureus* [3, 4]. Meropenem is mainly used to treat Bacterial meningitis [5] which increases the stability to degrade by Dehydropeptidase-I. eg: Merrem I.V, Meronem. Protein binding of about 2%. Metabolism excreted is unchanged; Route of elimination is 70% IV in urine over 12 hrs, $t^{1/2}$ [6] 1 hr adults & children 2 yrs of age. Toxicity in Mice and Rats I.V dose of (2200-4000mg/kg) causes dyspnea, convulsions.

Cefepime

It belongs to fourth generation cephalosporins [7] which are more resistant to β lactamases. Cefepime is usually reserved to treat

severe nosocomial pneumonia infections caused by multi-resistant micro-organisms (eg *Pseudomonas aeruginosa*) [8, 9, 10] empirical treatment of febrile neutropenia which is active against streptococci, methicillin-sensitive staphylococci but it is not active against MRSA. Cefepime has excellent penetration for CNS infections. eg: Maxipime, Maxcef, Cepimex. Protein Binding is of about 20%; Metabolism occurs in liver NMP and rapidly converted to NMP-N-Oxide.

Route of elimination $t^{1/2}$ 2(0.3) hrs, Clearance [11] is 120 mL/min [Healthy adult male receiving a single 30-minute IV infusions of cefepime], 3.3 +/- 1.0 mL/min/kg [Pediatric patients (2 months-11 years of age) receiving a single IV dose], Toxicity over dosage includes seizures, encephalopathy.

Piperacillin+Tazobactam

It belongs to the class Carboxypencillins and Ureidopencillins. They are acid liable, inhibits by cell wall synthesis and susceptible to β -lactamase [12, 13] and is not recommended for the treatment of bacterial meningitis. They act synergistically with amino glycoside antibiotics and is a good choice to treat surgical wound infections [14]. Volume of distribution is 101mL/min/kg [intravenous administration of 50 mg/kg (5-minute infusion) in neonates], not metabolized, Route of elimination as with other penicillins, Pipracil is eliminated primarily by glomerular filtration and tubular secretion; it is excreted rapidly as unchanged drug in high concentrations in the urine. Because Pipracil is excreted by the biliary route as well as by the renal route, it can be used safely in appropriate dosage in patients with severely restricted kidney function. $t^{1/2}$ 36-72 minutes. Clearance [15] is 32 - 41 mL/min / 1.73 m², 124 - 160 mL/min / 1.73 m² [older pediatric patients]. Used in combination with piperacillin to broaden the spectrum of piperacillin antibacterial action. Eg: Zosyn, Tazocin and Pipracil.

MATERIALS AND METHODS

Study Area and Period

The population of this study constitutes respondents in Andhra Pradesh, which covers all the super-speciality and multi-speciality hospitals. The Sample size constitutes of [N=128] per quarter were documented from 15 areas in Andhra Pradesh for a period of 6

months. The Sampling Unit consists of clinicians based on their specializations.

Study Design

The doctors prescribing the three most effective anti-bacterial drugs were Meropenem, Cefepime, Piperacillin+Tazobactam used in serious infections consists of General Physicians, Critical Care, General Surgeons, Gastro Enterologist, Orthopaedics, Paediatrician, Nephrologists, Gynecologists, Anaesthetist.

Data Collection Management

Research Methodology is the systematic way to solve the problem. Data collection plays an important role in survey analysis which is of two modes. Probably I selected both the modes. Firstly, Primary data a structured questionnaire was designed for the collection from the targeted respondents. Secondly, the other sources of data were from the text books and website has been the major source for reviewing journals, articles, blogs etc. An accurate data has been collected both qualitatively and quantitatively from the clinicians. Analyzing the depth of the research topic based on the given time framework, I selected (N=128) respondents. The collected data was tabulated and analyzed using percentage analysis which refers to ratio between two or more data and describes their relationship; descriptive statistics were used in order to meet the objective of the study.

Research Instrument

The research instrument is to analyze the preference order of the three anti-bacterial drugs (Piperacillin+Tazobactam, Cefepime, Meropenem). In order to make my research specific and to address the issue in the marketers point of view, conducted analysis on the three most efficacious drugs

- In what type of cases does the doctor prefer these drugs?
- The prescribed dosage and duration of these drugs during the diseased condition?
- Are there any specific conditions to avoid these drugs?

Ethical Consideration

Prior to the study an ethical clearance was obtained from various hospitals. Before data collection an official letter from the college explaining the purpose of the survey was submitted to the hospital administration for the collaboration during data collection and support of the administration in prior meeting with the doctors.

RESULTS AND DISCUSSION

When assessed on usage of antibiotics in serious infections, Out of 128 respondents reviews it was found out that

Usage of drugs based on the specialization, number of doctors, and super, multi-speciality hospitals were taken into consideration

General Physician's out of 32 clinicians, Piperacillin + Tazobactam (24 doctors), Cefepime (8 doctors). Critical Care out of 16 clinicians Piperacillin + Tazobactam (12 doctors), Cefepime (4 doctors). General Surgeons total 12 doctors prescribe Piperacillin + Tazobactam. Gastro-Enterologist out of 12 doctors, Piperacillin + Tazobactam (8 doctors) and Meropenem

(4 doctors). Orthopaedic Surgeons total 16 doctors prescribe Piperacillin + Tazobactam. Paediatricians out of 8 clinicians, Piperacillin + Tazobactam (4 doctors) and Cefepime (4 doctors). Nephrologist total 8 doctors prescribe Piperacillin + Tazobactam. Gynecologist total 16 doctors prescribe Piperacillin + Tazobactam. Anaesthetist total 8 doctors prescribe Piperacillin + Tazobactam. From the above data we can estimate that the most specialized doctors in super and multi speciality hospitals uses

- Piperacillin+Tazobactam as Ist line of drugs.
- Cefepime as IInd line of drugs.
- Meropenem as IIIrd line of drugs.

Note: When patients do not respond to usual medicines known as Ist line of drugs, doctors prescribe IInd or IIIrd line of drugs which usually costs more

Analysis of drugs used based on the % usage of doctors, % usage based on the specialization

Considering all the above details of 128 respondents, tabular columns were drawn in Table 1 and Table 2 below respectively

Table 1: Drugs used based on % usage of 128 doctors

Drugs	% Usage of 128 Doctors
Piperacillin +Tazobactam	84.38
Cefepime	12.50
Meropenem	3.123

Table 2: Percentage of Drugs used based on the Specialization*

Specialization*	Meropenem % of usage based on specialization*	Cefepime % of usage based on specialization*	Piperacillin+Tazobactam % of usage based on specialization*
General Physician	0	25	75
Critical Care	0	25	75
General Surgeon	0	0	100
Gastro -Enterologist	33.33	0	66.7
Orthopaedic Surgeons	0	0	100
Paediatrics	0	50	50
Nephrologist	0	0	100
Gynecologist	0	0	100
Anaesthetist	0	0	100

3.125% of doctors prescribe Meropenem: Out of which (33.33%) of Gastro Enterologist prescribe Meropenem to treat against complicated appendicitis and peritonitis caused by (*E.coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacteroides*, *Peptostreptococcus species*). 12.5% of doctors prescribe Cefepime: Out of which (25%) of General Physician's prescribe Cefepime for Febrile Neutropenia (*E.coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*). (25%) of Critical Care clinicians treat Respiratory tract infections and Uncomplicated skin/Skin structure infections caused by *Staphylococcus aureus*, (50%) of Paediatrician treat against Nosocomial pneumoniae caused by *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*.

84.38% of doctors prescribe Piperacillin +Tazobactam: Out of which (75%) of General Physician's treat Respiratory Tract Infections (RTI), Pneumonia (*Klebsiella pneumoniae*, *Streptococcus pneumoniae*), and Diabetic foot infections (*Staphylococcus aureus*). (75%) of Critical Care treat Respiratory infections and Uncomplicated skin/Skin structure infections caused by *Staphylococcus aureus* (100%) of General Surgeons and Anaesthetist prescribe to treat skin infections caused by *Staphylococcus aureus*, Pneumonia (*Klebsiella pneumoniae*, *Streptococcus pneumoniae*) (66.7%) of Gastro Enterologist prescribe to treat Moderate Sepsis, Appendicitis (complicated by rupture or abscess) and peritonitis caused by piperacillin-resistant, β - lactamase

producing strains of *E.coli* and the following member of the *B.fragilis* group: *B.fragilis*, *B.ovatus*, *B.thetaiotaomicron*, *B.vulgatus* (100%) of Orthopaedic Surgeons prescribe to treat Bone and Joint Infections caused by (Staphylococci, Streptococci). (50%) of Paediatrician prescribe to treat Neonatal sepsis and Nosocomial pneumonia caused by *Acinetobacter baumannii*, *Haemophilus influenzae*, *Kpneumoniae*, *Pseudomonas aeruginosa* (Note: Nosocomial pneumonia caused by *Pseudomonas aeruginosa* should be treated with an aminoglycoside). (100%) of Nephrologist treat Urinary Tract Infections caused by *E.coli*, *Klebsellia*. (100%) of Gynecologist treats Postpartum endometritis/Pelvic inflammatory disease caused by piperacillin-resistant β -lactamase producing strains of *Escherichia coli*. were depicted from Table 1 (Figure 1) and Table 2 (Figure 2) respectively,

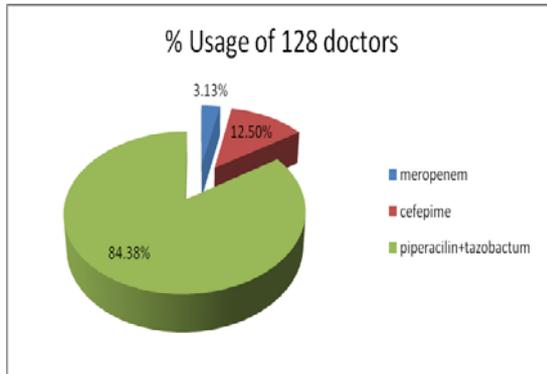


Fig. 1: % Usage of 128 Doctors treating Serious Infections.

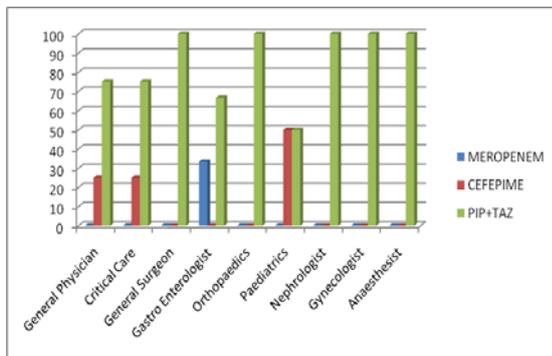


Fig. 2: % Usage based on the specialization

Usage of drugs based on the type of case, dosage and duration prescribed by the doctors

Meropenem:

Label claim (500mg, 1.0gm, 2.0gm), Single therapy, (15 -30 min), I.V 8hrs.

- Gastro Enterologist prescribes 1.0gm/kg I.V, TID (7-10 days) under severe abdomen Sepsis, Acute Abdomen infections, and Pancreatitis conditions.

Cefepime: Label Claim (250mg, 500mg, and 1000mg), Single therapy, (15-30 min),I.V/L.M 12hrs.

- General Physician prescribes 1.0 gm /kg I.V, BID (5-7 days) under LRTI /UTI, CAP, SSTI infections, Initial sepsis and Febrile Neutropenia.
- Critical Care prescribes 1.0gm /kg I.V, BID (5 -7 days) under RTI, Skin and soft tissue Infections and uncomplicated sepsis conditions.
- Paediatrician prescribes 500mg /kg I.V BID (7-10 days) under LRTI and Nosocomial Pneumonia.

Piperacillin + Tazobactam: Label Claim (1.0gm + 125 mg, 2.0gm + 250 mg, 4.5gm + 500mg), Combination therapy, 30 min, I.V 8hrs, not used in children below 12 years of age.

- General Physician prescribes 4.5 gm + 0.5 gm /kg I.V TID (7-10 days) under RTI, UTI, Abdomen sepsis, Pneumonia Infections and Diabetic foot infections.
- Critical Care prescribes 4.5 gm + 0.5 gm /kg I.V TID (7-10 days) under uncomplicated sepsis, Pneumonia, UTI, LRTI and Intra abdominal Sepsis.
- General Surgeon prescribes 4.5 gm + 0.5 gm /kg I.V TID (7-10 days) under skin and soft tissue infections and RTI conditions.
- Gastro Enterologist prescribes 4.5 gm + 0.5 gm /kg I.V TID (7-10 days) under moderate sepsis conditions.
- Orthopaedic Surgeons prescribes 4.5 gm + 0.5 gm/kg I.V TID (7-10 days) under Joint replacement surgeries and Bone-Joint infections.
- Paediatrician prescribes 4.5 gm + 0.5 gm/kg I.V TID (7-10 days) under Neonatal sepsis, LRTI, Nosocomial Pneumonia, UTI and sepsis conditions.
- Nephrologist prescribes 4.5 gm + 0.5 gm/kg I.V TID (7-10 days) under UTI infections
- Gynecologist prescribes 2.25 gm + 0.25 gm/kg I.V TID (4-5days) under UTI, Pelvic and Open wound / surgical infections.
- Anaesthetist prescribes 4.5 gm + 0.5 gm/kg I.V TID (7-10 days) under Pneumonia,UTI,LRTI and severe sepsis conditions

Analysis based on the type of case and % Usage of doctors

From the above information analysis based on the type of case and % Usage of doctors is shown below in Table 3 and Figure 3 is illustrated

Table 3: Based on the type of case and % Usage of Doctors

Based on the type of case	% Usage of Doctors
Sepsis	17.86
Severe Sepsis	14.29
UTI	25.00
CRTI,LRTI	8.33
Others	34.52

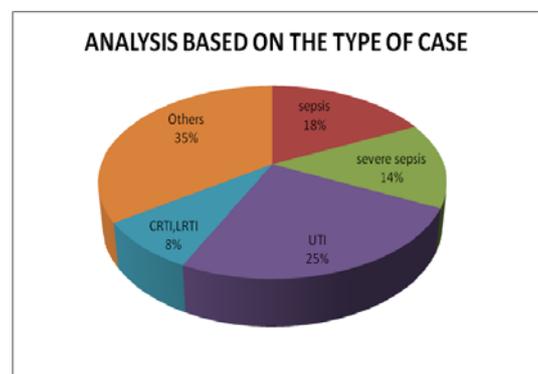


Fig. 3: Based on the type of case and % of usage of doctors

Any Specific conditions to avoid these drugs

Meropenem is avoided especially when the patient is suffering from Seizures whereas Cefepime and Piperacillin + Tazobactam are avoided under Hypersensitivity reactions and Renal failure (In such cases the dosage level is reduced by the Nephrologist for Clearance).

CONCLUSION

The drugs used for the treatment of serious infections (sepsis, severe sepsis, LRT, CRTI, UTI, others) were studied based on their pharmacological actions and market analysis which also include the thorough survey of usage of each above mentioned drug in the profilitic manner. The results were concluded based on the prescription of the disease. Piperacillin+Tazobactam was considered to be the Ist line, Cefepime as the IInd line followed by Meropenem as the IIIrd line drug. Finally I conclude when a competitor enters into the market they should consider the market availability of the products (domestic & generic) as per the cost and reliable to the patients based on less adverse effects, antibiotic resistance and ease of intake to the patients as per the demographical conditions.

CONFLICT OF INTERESTS

Declared None

ACKNOWLEDGMENT

I acknowledge this work to all the clinicians and management of various hospitals for their collaboration and assistance during data collection and I am very thankful to our college staff for their constant support and encouragement in providing their insightful comments.

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