ORIGINAL RESEARCH

Evaluation of the use of piperacillin/tazobactam (Tazocin®) at Hamad General Hospital, Qatar: are there unjustified prescriptions?

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Objectives: The aim of this study was to evaluate the appropriateness of piperacillin/tazobactam (Tazocin®; Pfizer, New York, NY) usage in our hospital.

Subjects and methods: This retrospective study was designed to involve all patients admitted to Hamad General Hospital and prescribed piperacillin/tazobactam as an empiric therapy from January 1 to March 31, 2008. The medical records of such patients were retrospectively reviewed and studied.

Results: During this period, 610 prescriptions were ordered for 596 patients. The main indication for initiation of Tazocin was sepsis (207/610; 34%). The overall rate of appropriateness of empirical therapy was 348/610 (57%). Most of the inappropriate prescriptions were in cases of aspiration pneumonia and abdominal infections, with inappropriate prescriptions found mostly in surgical wards (86%) and the surgical intensive care unit (66.7%). Septic work-up results showed positive cultures in 57% (345/610) of cases. There were 198/254 prescriptions (78%) where antibiotics were changed according to the sensitivity data to narrow-spectrum antimicrobials. In 56/254 (22%) cases, pathogens were susceptible to narrow-spectrum antibiotics even though piperacillin/tazobactam was continued.

Conclusion: Our study showed that there was an injudicious use of piperacillin/tazobactam at our hospital, evidenced by the significant number of inappropriate empiric prescriptions and inappropriate drug modifications, based on the results of microbial cultures and antibiograms.

Keywords: piperacillin/tazobactam, empiric therapy, appropriate use, broad-spectrum antibiotics

Introduction

The broadest-spectrum antibiotics, such as fourth-generation cephalosporins, piperacillin/tazobactam (Tazocin®; Pfizer, New York, NY), and carbapenems, play an important role in the empiric therapy of serious infections. Misuse of these antibiotics is common and costly,[1] as physicians often opt for broad-spectrum antibiotics when a narrower-spectrum agent would suffice.[2] Over-reliance on broad-spectrum agents is also thought to be an important contributor to growing worldwide antimicrobial resistance.[3] Many hospitals implement a range of measures to address these growing problems. One common measure is to adopt an antibiotic formulary and guidelines.[4] In our hospital, the therapeutic committee has issued an antibiotic policy.[5] Other methods include supervision of antibiotic use by infectious disease consultants and/or clinical pharmacists, provision of continuing education regarding appropriate anti-microbial drug use, implementation of automatic stop orders, and drug utilization evaluation.[1,6]

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Piperacillin/tazobactam is a β-lactam/β-lactamase inhibitor combination with a broad spectrum of antibacterial activity against most Gram-positive and Gram-negative aerobic bacteria and anaerobic bacteria. Tazocin is effective and well tolerated in patients with lower respiratory tract infections, intra-abdominal infections, skin and soft tissue infections, and febrile neutropenia.[7] Tazocin was approved by the therapeutic committee at Hamad General Hospital many years ago. Since that time, it has become one of the most-prescribed pharmaceuticals in our hospital. In 2008, there were 2600 prescriptions of this drug. The use of antimicrobial agents has been widely assessed in hospitals by measuring quantitative pharmacy data to calculate the number of defined daily doses per occupied bed-days, but this measurement does not indicate whether therapy was appropriate. Because of its high prescription volume and spiraling expenditure, this study was conducted to evaluate the appropriateness of Tazocin usage in our hospital.

Subjects and methods
Design and setting
This retrospective study was conducted at Hamad General Hospital, which is a tertiary center that covers all specialties except for hematology, oncology, and obstetrics. It includes six intensive care units that provide a full range of clinical services for different subspecialties.

Patients, diagnostic criteria, and data source
The study involved all patients admitted to Hamad General Hospital and prescribed Tazocin as an empiric therapy during a period of three months from January 1, 2008 to March 31, 2008, after being approved by the Medical Ethics Committee of the Hamad Medical Corporation. Patients were identified from the hospital's pharmacy records and then the medical records of these patients were retrospectively reviewed and studied. During this period, 981 prescriptions of Tazocin were ordered for 876 patients. Only 371 of these prescriptions were used to treat documented infections, whereas 610 were prescribed initially as empiric therapy for suspected infections. These 610 cases were the subject of this study. Tazocin prescription was deemed appropriate if:

- it was selected as an empirical therapy in accordance with hospital's guidelines[5]
- it was switched to an alternative antibiotic with a narrow spectrum after receipt of culture and susceptibility data
- the dose was in accordance with the hospital's guidelines
- it was discontinued once culture data were negative

- it was discontinued once culture data showed a resistant organism.

If one of these conditions was not met, the prescription was considered inappropriate.

Data collection and analysis
The medical record of each patient was reviewed to retrieve patient demographic data and provisional diagnosis, and whether Tazocin as empirical therapy was appropriate according to the criteria above. The gathered information was transferred to the computer utilizing the Epi Info™ 2000 (Centers for Disease Control and Prevention, Atlanta, GA) software. Data were analyzed using simple statistics.

Results
During the period of study, 610 prescriptions were ordered for 596 patients. The mean age of patients was 62.8 ± 16.8 years (25–93 years) and 79% (483/610) of them were male.

Table 1 describes the indications for which Tazocin was prescribed as an empiric treatment for suspected infections. The main indication for initiation of Tazocin was sepsis (207/610; 34%). Table 2 describes the appropriateness of Tazocin therapy. The overall rate of appropriateness of empirical therapy was (348/610; 57%). Most of the inappropriate prescriptions were in cases of aspiration pneumonia, peritonitis, acute cholecystitis, community-acquired pneumonia, skin and soft tissue infections, and community-acquired urinary tract infections (Table 1).

Patients were distributed in different wards. The wards in which inappropriate prescription patterns were most frequently observed included the surgical ward (86%) and the surgical intensive care unit (66.7%). Table 3 summarizes the distribution of the patients in different wards in the hospital in relation to appropriate use of Tazocin.

Septic work-up results showed positive cultures in 57% (345/610) of episodes. The most frequently identified microorganisms were Gram-negative bacilli, which included *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter* species, and others. The identified microorganisms showed resistance to Tazocin in 30/345 cases (8.7%) and they were sensitive to Tazocin as well as other antimicrobials with a narrow spectrum in 254/345 cases (73.6%). However, the isolates were sensitive to Tazocin and other broad-spectrum antibiotics (cefepime and meropenem) only in 61/345 cases (17.7%). There were 198/254 prescriptions (78%) where antibiotics were changed according to the sensitivity data to narrow-spectrum antimicrobials, whereas in 56/254 cases (22%) pathogens were susceptible

Table 1 Conditions for which Tazocin® was prescribed empirically and appropriateness of prescription

Provisional diagnosis	Total (column)	Appropriate	Inappropriate	Total (row)
Community-acquired UTI	49 (8.0%)	13 (25.0)	36 (75.0)	49 (100.0)
Peritonitis	24 (4.0%)	0 (0.0)	24 (100.0)	24 (100.0)
Acute cholycystitis	12 (2.0%)	0 (0.0)	12 (100.0)	12 (100.0)
Aspiration pneumonia	49 (8.0%)	0 (0.0)	49 (100.0)	49 (100.0)
Community acquired pneumonia	43 (7.0%)	0 (0.0)	43 (100.0)	43 (100.0)
Febrile neutropenia	12 (2.0%)	12 (100.0)	0 (0.0)	12 (100.0)
Line related sepsis	55 (9.0%)	49 (89.0)	6 (11.0)	55 (100.0)
Nosocomial pneumonia	61 (10.0%)	61 (100.0)	0 (0.0)	61 (100.0)
Nosocomial UTI	12 (2.0%)	6 (50.0)	6 (50.0)	12 (100.0)
Peritonitis with CAPD	12 (2.0%)	0 (0.0)	12 (100.0)	12 (100.0)
SBP	12 (2.0%)	0 (0.0)	12 (100.0)	12 (100.0)
Sepsis	207 (34.0%)	207 (100.0)	0 (0.0)	207 (100.0)
Skin and soft tissue infection	31 (5.0%)	0 (0.0)	31 (100.0)	31 (100.0)
Others	31 (5.0%)	0 (0.0)	31 (100.0)	31 (100.0)
Total	610 (100.0%)	348 (57.0)	262 (43.0)	610 (100.0)

Abbreviations: UTI, urinary tract infection; CAPD, continuous ambulatory peritoneal dialysis; SBP, spontaneous bacterial peritonitis.

to narrow-spectrum antibiotics even though Tazocin was continued, reflecting inappropriate usage of this antibiotic. In a few prescriptions (3/254; 1.2%), Tazocin was continued despite the microbiological results showing that the pathogens were resistant to the drug. Among cultured negative cases (265/610; 43%), Tazocin was continued in most cases (160/265; 60%). The reasons for Tazocin continuation despite negative cultures were unclear. The dose adjustment of Tazocin was achieved perfectly in all patients. Table 2 summarizes the appropriateness of Tazocin therapy.

Discussion

The over-utilization of Tazocin compared with other broadest-spectrum antibiotics, which increases the probability of the emergence of resistant organisms,[3] in addition to the available evidence from a previous study[8] that has

Table 2 Summary of Tazocin® usage appropriateness

Data	Appropriate	Inappropriate
Initial use as empirical therapy in accordance with hospital's guidelines	348/610 (57%)	262/610 (43%)
Switching to an alternative antibiotic with narrow spectrum after receipt of culture and susceptibility data	198/254 (78%)	56/254 (22%)
Dosing in accordance with the hospital's guidelines	610 (100%)	0.0%
Dose adjustment in renal impairment	213/213 (100%)	0.0%
Discontinuation once culture data were negative	105/265 (40%)	160/265 (60%)
Discontinuation once culture data showed resistant organism	27/30 (90%)	3/30 (10%)

showed emerging resistance to Tazocin among Gram-negative microorganisms, is alarming and prompted us to conduct this study, which is the first to evaluate the usage of Tazocin in our hospital.

The choice of Tazocin as an empiric therapy depends on the knowledge of the most common causative bacteria in different conditions and the reported efficacy of this drug. Therefore, to regulate empirical usage of antibiotics, many institutes such as ours have developed a set of guidelines. In our hospital these guidelines have been updated periodically by consensus among experts (microbiologists, clinicians, and pharmacists) based on local studies and annual surveillance. Despite implementation of these guidelines, there were a significant number of inappropriate empiric prescriptions of Tazocin, most probably due to physicians being unaware of the hospital's guidelines and/or their difficulty in recalling these guidelines during busy working hours. Other reasons for inappropriate empirical therapy include uncertainty of differential diagnoses; complex comorbidities; and lack of training, experience, or confidence of the physicians in charge.

As noted, 73.6% of positive-culture cases were suitable for modification to narrow-spectrum antimicrobials, but 22% of the prescriptions remained unchanged. Moreover, three prescriptions were continued despite the microbiological results showing that the pathogens were resistant to the drug. These findings may be attributed to physicians' lack of knowledge or to their overlooking the culture results and antibiotic sensitivity profiles.[9] Modification of empiric antibiotic therapy based on the results of microbial cultures and antibiograms will help to reduce costs, decrease the incidence of superinfection, and minimize the development of resistance.[10]

Table 3 Departments in which the drug was prescribed empirically

Ward	Total (column)	Appropriate	Inappropriate	Total (row)
CCU	31 (5.0%)	25 (80.4%)	6 (19.6%)	31 (100.0%)
Medical	341 (56.0%)	183 (53.6%)	158 (46.4)	341 (100.0%)
MICU	159 (26.0%)	116 (73.0%)	43 (27.0%)	159 (100.0%)
SICU	18 (3.0%)	6 (33.3%)	12 (66.7%)	18 (100.0%)
Surgical	43 (7.0%)	6 (14.0%)	37 (86.0%)	43 (100.0%)
TICU	18 (3.0%)	12 (66.7%)	6 (33.3%)	18 (100.0%)
Total	610 (100%)	248 (57.0%)	262 (43.0%)	100 (100.0%)

Abbreviations: CCU, coronary care unit; MICU, medical intensive care unit; SICU, surgical intensive care unit; TICU, trauma intensive care unit.

Interestingly, many initial empirical therapy courses (265/610; 43%) were found to be culture-negative, which is higher than one would expect. This could be explained partly by the fact that the majority of our patients were elderly and presented with vague symptoms mimicking sepsis. These vague symptoms are usually attributed to noninfectious disorders such as renal impairment, hyperglycemia, metabolic acidosis, starvation, and dehydration.

Among cultured negative cases, Tazocin was continued in most cases (160/265; 60%). This is similar to the report of Ahkee et al,[11] who reported that one of the common reasons for prescribing antibiotics inappropriately is giving them to patients without documented infection. The reasons for Tazocin continuation in our study despite negative cultures were unclear. This requires more study.

This study has some limitations. Firstly, it was retrospective rather than prospective and this design did not allow us to obtain additional details, such as the reason for Tazocin continuation despite negative cultures. Secondly, we focused on cases occurring over a 3-month period, which may not have been enough time for accurate judgment. Thirdly, due to a lack of studies on Tazocin worldwide, we could not benchmark and compare our results with other centers.

Conclusion

Our study has shown that there were unjustified prescriptions at our hospital, evidenced by the significant number of inappropriate empiric prescriptions and inappropriate drug modification based on the results of microbial cultures and antibiograms. We suggest further prospective studies to confirm these findings and to explain the reasons for Tazocin continuation despite negative cultures. To improve the appropriateness of Tazocin prescription in our hospital, we recommend:

- dissemination of the implemented guidelines, via widespread publication and staff education
- rationalization of the use of Tazocin in different hospital units, with a special focus on both initial empirical therapy

and modification of this therapy once microbiological results become available
- ongoing annual surveillance, to monitor progression of resistance to this drug
- restrictive measures, ie, infectious disease team consultation should be mandatory prior to prescription of this drug.

Disclosure

The authors report no conflicts of interest in this work.

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