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ORIGINAL ARTICLE

Cost-minimization analysis of imipenem/cilastatin versus meropenem in moderate to severe infections at a tertiary care hospital in Saudi Arabia

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Meropenem

Abstract *Aim:* The aim of this study was to compare the costs of management of moderate to severe infections in patients treated with imipenem/cilastatin (IC) and meropenem (MEM). Pharmacoeconomic studies in Saudi Arabia are scarce. The current hospital formulary contains 2 carbapenems: IC and MEM. These antibiotics share a similar spectrum of activity. There are conflicting reviews with regard to the relative cost-effectiveness of these two agents. *Methods:* A retrospective, single-centre cohort study of 88 patients of IC versus MEM in moderate to severe infections was performed, applying cost-minimization analysis (CMA) methods. In accordance with CMA methods, the assumption of equivalent efficacy was first demonstrated by literature retrieved and appraised. Adult patients (⩾18 years old) diagnosed with moderate to severe infections, including skin and skin structure infections (SSIs), sepsis, intra-abdominal infections (IAIs), respiratory tract infections, urinary tract infections (UTIs) and hospital-acquired infections (HAIs), who were prescribed IC 500 mg every six hours intravenously (2 g per day) or MEM 1 g every eight hours (3 g per day), were included in the study. Only direct costs related to the management of the infections were included, in accordance with a payer perspective. *Results:* Overall there was no difference in

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the mean total daily costs between IC (SAR 4784.46, 95% CI 4140.68, 5428.24) and MEM (4390.14, 95% CI 3785.82, 4994.45; $p = 0.37$). A significantly lower medicine acquisition cost per vial of IC was observed when compared to MEM, however there was a significantly higher cost attached to administration sets used in the IC group than the MEM group. Consultation, nursing and physician costs were not significantly different between the groups. No differences were observed in costs associated with adverse drug events (ADEs). *Conclusion:* This study has shown that while acquisition costs of IC at a dose of 500 mg q6 h may be lower than for MEM 1 g q8 h, mean total costs per day were not significantly different between IC and MEM, indicating that medicine costs are only a small element of the overall costs of managing moderate to severe infections.

1. Introduction

As in almost every health system, medication costs at the King Abdulaziz Hospital (KAH) have increased noticeably over time (Saggabi, 2012). High prices of essential medicines are a heavy burden on the government budget (Saggabi, 2012). Policymakers are thus in search of the most cost-effective options for the government and society as a whole.

Data from KAH show that the carbapenem antibiotics were the third most expensive pharmacological class procured during 2009. The current hospital formulary lists two carbapenems: the fixed-dose combination of imipenem/cilastatin (IC) and meropenem (MEM). MEM is restricted to infection control physicians, while IC is restricted to infection control, intensivists and haematology/oncology practitioners. These antibiotics share a similar spectrum of activity, but the unit cost of IC (500 mg/500 mg) is less than that for the equipotent dose of MEM (1 g). There are conflicting reviews with regard to the relative cost-effectiveness of these two medicines (Attanasio et al., 2000; Edwards et al., 2006).

An unpublished pharmacoeconomic review, at the Ministry of National Guard Health Affairs, showed that an interchange programme, substituting MEM with IC, would lead to a cost saving of 2,306,257 Saudi Riyals (SARs) per year (614,309 US dollars per year). Hospital antimicrobial usage data since 2004 showed that usage of IC had been markedly lower than the usage of MEM. There have been limited applications of pharmacoeconomic evaluations in Saudi Arabia (Al Aqeel and Al-Sultan, 2012). It would be appropriate, therefore, to test the economic impact of the proposed substitution as well as the main factors influencing hospital costs, in this setting, based on pharmacoeconomic principles. In this regard, cost-minimization analysis (CMA) could provide an estimate of the economic impact of these therapeutically equivalent medicines, using local Saudi Arabian data.

The aim of this study was to contribute to the rational selection of medicines, in order to achieve efficiencies and better patient outcomes, by focusing on high-cost medicines used in the Saudi Arabian health system.

2. Background

In 2012, total annual expenditure on MEM at KAH placed it in the top 10 medicines at the institution in value terms. The Department of Infection Control, Department of Microbiology and Pharmacy attempted to minimize usage of MEM by suppressing mention of this agent in sensitivity reports appearing in the hospital's electronic health information system. This was implemented in an attempt to encourage usage of alternative antibiotics, including IC. The Pharmacy and Therapeutics Committee (PTC) also restricted the use of MEM to infection control practitioners only. IC was restricted to infection control, intensivists and haematology/oncology practitioners. The Infection Control Department developed usage guidelines for IC and MEM. An unpublished pharmacoeconomic review examined the acquisition costs of the study drugs, but did not include the resource costs associated with the primary infection. A CMA was therefore proposed in an attempt to investigate the overall costs associated with the use of these two clinically equivalent medicines.

2.1. Pharmacoeconomic principles

The field of pharmacoeconomics identifies the costs and consequences of alternative medicines therapy in order to make the best possible decision, while ensuring the maximum benefit and efficiency of budgets or resources (Drummond, 2006). In this study, a CMA approach was selected, which assumes that the consequences are clinically equivalent and then determines the least costly alternative (Newby and Hill, 2003). Studies on the local population may be more applicable to the context of Saudi Arabia and hence a study of this nature was considered.

2.2. Pharmacology

IC and MEM are both carbapenem antibiotics. These beta-lactam antibiotics are similar to penicillins and cephalosporins, but differ in their structure. Carbapenems inhibit bacterial cell wall synthesis. Both IC and MEM exhibit activity against a wide range of Gram-positive and Gram-negative aerobic and anaerobic bacteria.

The first carbapenem (imipenem) became commercially available in 1985 for the treatment of complex microbial infections (Papp-Wallace et al., 2011). The fixed-dose combination IC (including the dehydropeptidase inhibitor cilastatin) has been marketed by Merck Sharp and Dome with the trade name Tienam® in Saudi Arabia (Anonymous, 2013). The United States Food and Drug Administration (FDA) has approved the dose of IC from between 250 mg q6 h to a maximum of 1 g q8 h, depending on the severity of the infection. The dose should be adjusted in patients with impaired renal function. MEM is a broad spectrum carbapenem, subsequently approved by the US FDA (Mohr, 2008; Baldwin et al., 2008). It has been marketed by AstraZeneca in Saudi Arabia as Meronem®

(Anonymous, 2013). The dose should be adjusted in patients with compromised renal function (Merrem, 2006). The FDA-approved MEM dosage for mild to severe infections varies from 500 mg to 1 g every six to eight hours.

3. Literature review

In order to justify the CMA approach used in this study, a literature review was first conducted to justify the *a priori* assumption of clinical equivalence of IC and MEM in the types of infections treated and the doses recommended in the KAH guidelines.

3.1. Literature search approach and methods

The sources used included the Cochrane Library, Medline database, Trip database and Google Scholar. The search terms employed included: efficacy, safety, adverse reactions, effectiveness, pharmacoeconomic, bacterial infections, skin infections, sepsis, urinary tract infections, respiratory tract infections, hospital-acquired infections, meropenem and imipenem.

Randomised controlled trials (RCTs) were considered the gold standard when comparing IC to MEM. However, systematic reviews, meta-analyses, pharmacoeconomic studies and other review articles were also retrieved. Studies were critically appraised for quality and relevance using the "Critical appraisal skills programme, United Kingdom" tool (Singh, 2013), where the full text could be retrieved.

Studies published in any language since the year 1995 were considered, although only those provided in English or in English translation could be included. The searches were last updated in October 2013.

3.2. Literature retrieved and appraised

A total of 28 relevant studies were retrieved, matching the search criteria and applicable to the international context. No studies conducted in Saudi Arabia could be found. The search found two meta-analyses, one systematic review (without meta-analysis), 12 RCTs, one prospective cohort study, and one retrospective cohort study that supported the position of clinical equivalence between IC and MEM. The six studies that did not show clinical equivalence were a pharmacoeconomic review, two systematic reviews and three RCTs. The present study evaluated IC at a dose of 500 mg q6 h versus MEM 1 gm q6 h. This dosage has been supported by the KAH antimicrobial guidelines (MNGHA, 2012) as well as the US FDA (Merrem, 2006; Primaxin, 2006). This choice is also supported by a systematic review (Zhanel et al., 1998). Some studies could not be reviewed in detail, either due to being in a foreign language or where an unclear conclusion was recorded.

The key findings of this appraisal provided convincing evidence of the clinical equivalence of IC and MEM. These findings are summarized in Table 1:

4. Methods

4.1. Type of research

This study was a retrospective, single-centre cohort employing CMA principles. The CMA assumes that consequences are equivalent while seeking the least expensive alternative (Dakin and Wordsworth, 2013; Walley and Haycox, 1997).

Table 1 Summary of critical appraisal.

	Critical appraisal findings	Supported by
1	IC clinically equivalent to MEM in patients with IAI	No difference in clinical efficacy supported by studies (Attanasio et al., 2000; Zhanel et al., 1998; Badia et al., 1999; Zanetti et al., 1999; Geroulanos, 1995; Beketov et al., 2003; Colardyn and Faulkner, 1996)
2	IC clinically equivalent to MEM in SSI	No difference in clinical efficacy supported by studies (Colardyn and Faulkner, 1996; Embil et al., 2006; Fabian et al., 2005; Nichols et al., 1995)
3	IC clinically equivalent to MEM in LRTI	No difference in clinical efficacy supported by studies (Colardyn and Faulkner, 1996; Xiao-Ju et al., 2001; Xiao et al., 2010; Song et al., 2001; Hou et al., 2002; Verwaest, 2000)
4	IC clinically equivalent to MEM in UTI	No difference in clinical efficacy supported by studies (Colardyn and Faulkner, 1996; Hou et al., 2002; Cox et al., 1995)
5	IC clinically equivalent to MEM in sepsis	No difference in clinical efficacy supported by studies (Verwaest, 2000; Kuo et al., 2000)
6	IC bacteriologically equivalent to MEM	No difference in bacteriological outcomes supported by studies (Attanasio et al., 2000; Geroulanos, 1995; Song et al., 2001; Cox et al., 1995; Kuo et al., 2000)
7	IC as safe as MEM	No difference in adverse drug events supported by studies (Attanasio et al., 2000; Zanetti et al., 1999; Geroulanos, 1995; Colardyn and Faulkner, 1996; Embil et al., 2006; Fabian et al., 2005; Nichols et al., 1995; Xiao et al., 2010; Hou et al., 2002; Verwaest, 2000; Cox et al., 1995; Kuo et al., 2000; Hoffman et al., 2009)
8	IC less costly than MEM	IC less costly than MEM supported by studies (Attanasio et al., 2000; Zhanel et al., 1998; Badia et al., 1999; Beketov et al., 2003)
9	IC 500 mg q6 h and MEM 1 gram q8 h	This dosage supported by Zhanel et al. (1998), United states FDA (Merrem, 2006; Primaxin, 2006) and our hospital Antimicrobial guidelines (MNGHA, 2012)

Key: IAI = intra-abdominal infection, SSI = skin and skin structure infection, LRTI = lower respiratory tract infection, UTI = urinary tract infection, IC = imipenem/cilastatin, and MEM = meropenem.

4.2. Study design

A CMA of IC versus MEM in moderate to severe infections was conducted at the KAH, Al-Ahsa (a 300 bed tertiary care centre). Between January 2012 and December 2012, all patients receiving IC 500 mg every six hours and MEM 1 g every eight hours for moderate to severe infection were included in the study. The study set out to capture 100 patient files with 50 patients in each arm, based on the estimated census of patients treated with these medicines in a calendar year.

The perspective of the economic evaluation was that of the provider or payer, in this case the Ministry of National Guard in Saudi Arabia that provides health-care to eligible dependents.

4.3. Study population

The inclusion criteria applied were: adult patients ($\geqslant$18 years old); patients diagnosed with moderate to severe infection, including SSI, sepsis, IAI, respiratory tract infections, UTI and HAI who were prescribed IC 500 mg every six hours intravenously (2 g per day); patients diagnosed with moderate to severe infection, including SSI, sepsis, IAI, respiratory tract infections, UTI and HAI who were prescribed MEM 1 g every eight hours intravenously (3 g per day).

The exclusion criteria applied were: those that were pregnant; with known or suspected meningitis; diagnosed with microorganisms resistant to IC or MEM; patients with a documented hypersensitivity or prior contraindication to IC or MEM.

4.4. Data collection

Data on patients' gender, age, weight, diagnosis, medical history, laboratory test results (including renal function and haematological status), recorded comorbid illnesses and previous medicines allergies, prescribed antifungals or antibiotics and microbiological tests were extracted from the hospital's electronic medical record. Information about consultant and physician visits was extracted from the paper-based physician notes, as were clarifications of the recorded diagnosis in cases where electronic records were incomplete. The documented outcomes were the length of hospitalization, length of antibiotic stay (LOAS: defined as the number of hospital days during which the patient was being treated for the diagnosed infection, including any treatment associated with treatment failure or related ADEs), and the resource consumption (limited to direct medical costs of managing the primary infection, based on the payer perspective).

4.5. Statistical analysis

The primary objective of the study was to compare the costs of management of moderate to severe infections in patients treated with IC and MEM. Descriptive statistics were presented as mean $\pm$ standard deviation for all continuous variables (e.g., age) while number (%) were reported for all categorical variables (e.g., gender). Bivariate analysis was performed by using Independent Sample *t*-test or Mann Whitney U-test whenever appropriate to compare the mean for all the continuous variables (e.g., age) between two groups (IC vs. MEM). Pearson Chi-Square test or Fisher exact test, as appropriate, were used to compare the proportion for all the categorical variables (e.g., gender) between the two groups. A two sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (Statistical Package for social sciences version 21).

4.6. Definitions

The diagnosis of moderate to severe infection, as described in the inclusion criteria, was based on the treating physician's documented clinical decision. In the case that the diagnosis was not clear, the patients' medical record was used to confirm the primary infection. Clinical success was dependent on the source of infection and defined by clinical improvement in signs and symptoms that would warrant resolution of fever or clinical signs of infection, discontinuation of antibiotics or discharge from the hospital without re-admission within 10 days or eradication of baseline positive microbiological pathogens. Evidence of the outcomes in each case was documented by the attending physician in the clinical notes.

Adverse drug events (ADEs) associated with IC or MEM were identified based on physician documentation and the records extracted from the hospital information system. The following circumstances were considered to be indicative of an ADE associated with IC or MEM: seizures, skin reactions, gastrointestinal disturbances, changes in liver function tests of more than 3 times the upper normal limit and changes in renal function (to a creatinine clearance less than 50 ml/min).

4.7. Costing

Pricing data were obtained from the financial section of the hospital's business centre. National drug prices were obtained from the Saudi Food and Drug Authority (SFDA) Human Drug List (http://www.sfda.gov.sa). The prices used were those in effect in October 2013. Direct medical costs included the costs of medications, laboratory tests, health care provider costs, hospitalization costs, consumables and administration costs. Direct non-medical costs (transportation and food) were not included in the study. Indirect medical costs (lost income) and intangible costs (pain and suffering) were excluded as incompatible with the perspective of the present study. Costs associated with support personnel such as maintenance, housekeeping, patient escort and administration were assumed to be fixed and were not included in the study. Laboratory data unrelated to the primary infection or super infections were not considered in the study. Investigators' and data collectors' fees were excluded. Discounting was not considered as the study period was for a single year. Pricing was in Saudi riyals (SARs). One SAR has been fixed at approximately 0.27 United States dollars (USD) for the last 10 years.

4.8. Pharmacoeconomic analysis

The perspective was that of the provider or payer, a government institute. The study period began at the point the primary infection was diagnosed. The LOAS was used to determine the time period of the costing analysis.

One-way sensitivity analysis was performed, in Microsoft® Excel 2010, by increasing and decreasing each parameter by 20%, while observing the impact on the results. A threshold analysis was performed, in Microsoft® Excel using 'what-if-analysis'.

4.9. Ethics

The protocol received approval from the King Abdullah International Medical Research Centre (reference number RRE12/011) eastern region of Saudi Arabia, as well as the Biomedical Research Ethics Committee at the University of KwaZulu–Natal in South Africa (reference number BE: 273/13).

5. Results

Although it was planned to include 50 patients in each group from 1 January 2012 until 31 December 2012, IC was prescribed to only 45 patients on IC during this period. One file could not be accessed as it was locked by the Health Information Management Department. Only 44 patients on MEM met the inclusion and exclusion criteria. In total, six patients were excluded from the study, due to diagnosis with meningitis ($n = 1$), pregnancy ($n = 1$), being under 18 years of age ($n = 1$), files being locked ($n = 2$) and administration of only a single dose ($n = 1$). A total of 44 patients receiving IC and 44 receiving MEM could therefore be evaluated.

5.1. Baseline characteristics

Baseline characteristics are summarized in Table 2. There were no significant differences in baseline characteristics between the groups.

5.2. Number of hospital days

There was a significant greater number of mean critical care days in the IC group compared to the MEM group ($p = 0.030$). However, the mean number of step-down days ($p = 0.375$), mean general ward (GW) days ($p = 0.472$) and LOAS ($p = 0.212$) showed no significant difference.

Table 2 Baseline characteristics.

	IC ($n = 44$)	MEM (n = 44)	P value
Age in years	65.64 ± 19.04	64.11 ± 21.28	0.724
Weight in kg	71.31 ± 15.81	68.80 ± 21.92	0.538
Height in cm	159.32 ± 11.15	157.82 ± 10.06	0.509
Male (%)	21 (47.73%)	20 (45.45%)	0.831

Results are expressed as mean ± standard deviation, and number (%).

5.3. Clinical characteristics

Clinical success rates and other clinical parameters are shown in Table 3 and were not statistically different between IC and MEM.

5.4. Adverse drug events (ADEs)

Gastrointestinal ADEs occurred in 1 (2.3%) of the patients on IC and 3 (6.8%) of the patients on MEM. General ADEs occurred in 1 (2.3%) patient on IC and 1 (2.3%) patient on MEM. Laboratory ADEs occurred in 5 (11.4%) patients in the IC group, compared with 6 (13.6%) patients in the MEM group. One case of seizure associated with IC was documented.

5.5. Hospital resources

Hospital resources showed no significant difference in the mean number of consultant visits ($p = 0.088$) and mean GW nurse days ($p = 0.642$). The mean pharmacist time (in min) was significantly higher in the IC group compared to the MEM group ($p = 0.004$) as well as the mean pharmacy aide time ($p = 0.004$). The mean number of administration sets used in the IC group was also significantly higher than in the MEM group ($p = 0.001$).

5.6. Economic evaluation

Resource utilization costs are listed in Table 4 as the mean resource cost per day. Comparison of the mean daily costs

Table 3 Clinical characteristics.

	IC ($n = 44$)	MEM ($n = 44$)	P value
Clinical success	26 (59.1%)	28 (63.6%)	0.661
Peak temperature in °C	37.98 ± 0.82	37.89 ± 0.78	0.597
WBC 10^9 L	19.27 ± 10.89	22.57 ± 23.44	0.401
Normal renal function	35 (79.5%)	34 (77.3%)	0.796
Moderate renal impairment	9 (20.5%)	10 (22.7%)	0.796
Number of positive skin infections	7 (15.9%)	7 (15.9%)	0.99
Number of positive sepsis cases	13 (29.5%)	16(36.4%)	0.496
Number of positive IAIs	5 (11.4%)	3 (6.8%)	0.458
Number of positive LRTIs	9 (20.5%)	7 (15.9%)	0.580
Number of positive UTIs	21 (47.7%)	22 (50.0)	0.831
Number of positive HAIs	16 (36.4%)	9 (20.5%)	0.098

Key: IC = imipenem/cilastatin; MEM = meropenem WBC = white blood cell count; IAI = intra-abdominal infection; LRTI = lower respiratory tract infection; UTI = urinary tract infection; HAI = hospital acquired infection. Results are expressed as mean ± standard deviation, and number (%).

Table 4 Resource utilization costs.

Average daily costs	IC mean	MEM mean	*P* value
CCU	1022.73 ± 706.73	784.09 ± 757.89	0.130
Step-down	572.73 ± 437.95	572.73 ± 437.95	0.99
GW	372.16 ± 218.16	465.91 ± 127.49	0.016
Vials	250.63 ± 41.34	393.48 ± 89.99	<0.001
Administration sets	39.16 ± 6.46	28.00 ± 4.57	<0.001
Laboratory tests	904.96 ± 810.29	761.32 ± 708.77	0.379
Laboratory cultures	86.61 ± 40.42	129.64 ± 105.78	0.014
CCU consult	681.82 ± 471.16	522.73 ± 505.26	0.13
GW consult	205.26 ± 297.77	200.47 ± 284.15	0.939
Staff physician	264.48 ± 136.98	215.55 ± 96.39	0.056
CCU nurse	204.55 ± 141.35	156.82 ± 151.58	0.13
GW nurse	92.88 ± 25.49	93.18 ± 25.50	0.956
Pharmacist	64.08 ± 10.57	46.82 ± 10.71	<0.001
Pharmacy aide	21.36 ± 3.52	15.61 ± 3.57	<0.001
ADE	1.05 ± 3.48	3.78 ± 18.24	0.333
Totals	4784.46 ± 2117.50	4390.13 ± 1987.70	0.37

Key: IC = imipenem/cilastatin; MEM = meropenem; CCU = critical care unit; GW = general ward; ADE = adverse drug events. Results are expressed as mean ± standard deviation.

using independent sample – *T* tests demonstrated no significant difference in terms of mean daily critical care unit (CCU) and step-down costs. A significant lower medicine acquisition vial cost was observed for IC (SAR 250.63, 95% CI 238.06–263.20) compared to MEM (SAR 393.48, 95% CI 366.12–420.84) ($p < 0.001$). However there was a significantly higher cost attached to administration sets in the IC group (SAR 39.16, 95% CI 37.2–41.13) than in the MEM group (SAR 28.00, 95% CI 26.61–29.39) ($p < 0.001$).

Overall there was no difference in the mean total daily costs between IC (SAR 4784.46, 95% CI 4140.68–5428.24) and MEM (SAR 4390.13, 95% CI 3785.82–4994.45) ($p = 0.37$), as shown in Table 4.

One-way sensitivity analysis showed that the parameters which exerted the greatest change in the mean total cost were the number of CCU days, laboratory tests and consultation charges (as shown in Fig. 1).

The threshold analysis found that variations in the number of ADEs, vial costs, administration costs and pharmacists' costs did not affect the conclusion even if the input value of each of the acquisition costs parameter was set at SAR 0.00.

6. Discussion

Several factors prompted the need for a pharmacoeconomic evaluation of IC and MEM. These included an institutional review of antimicrobial restriction and concerns about usage and costs. Most importantly, interchanging MEM with IC was thought to be able to lead to a cost saving of more than two million Saudi Riyals, as the acquisition costs of IC were noted to be less than those for MEM (SAR70.4 versus SAR 151.26 per vial). In addition, published pharmacoeconomic evaluations are limited in Saudi Arabia (Al Aqeel and Al-Sultan, 2012). To our knowledge, no published pharmacoeconomic evaluations comparing IC and MEM in adult patients have been conducted in Saudi Arabia. There have been several international pharmacoeconomic evaluations done (Attanasio et al., 2000; Edwards et al., 2006;

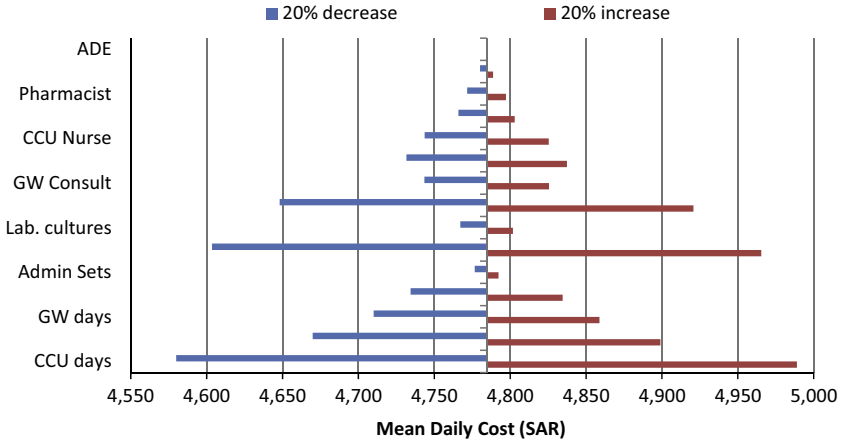

Figure 1 One way sensitivity analysis with IC (mean value = SAR 4784.46). Key: IC = imipenem/cilastatin; SAR = Saudi Arabian riyal; CCU = critical care unit; GW = general ward; ADE = adverse drug events. Results are expressed as mean ± standard deviation.

Badia et al., 1999), but with conflicting results. Using data based on the local perspective therefore had the potential to provide insight into the factors influencing local practice and medicines selection. Government institutions in Saudi Arabia, providing free medical treatment, may adopt similar costing strategies that are unique to this region.

At a dose of 500 mg q6 h (cost = SAR 281.60 per day), IC is an attractive alternative to MEM 1 gram q8 h (cost = SAR 453.78 per day), particularly in mild to moderate infections.

In the cohort of patients followed for this study, clinical success rates were not significantly different. The number of positive infections appeared similar. LOAS was not statistically different in both groups. The clinical efficacy data cohort was therefore in agreement with the literature justifying clinical equivalence.

The overall ADEs were not significantly different between the groups. It was found, though, that ADEs were under-reported. Although more patients had gastrointestinal ADEs in the MEM group, this was not significantly different when compared to IC. These were mainly antibiotic-associated diarrhoea, resulting in *C. difficile* culture being taken. One patient on IC experienced a seizure. Concern about this adverse effect has prompted the avoidance of IC among health care workers in our hospital. It must be pointed out that Hoffman et al. found no difference in seizure rates between patients treated with IC and MEM (Hoffman et al., 2009). These authors noted that elderly patients, patients with low body weight, at risk of CNS disease, those with a history of seizure and those with renal dysfunction appear to be at increased risk of drug-related seizures. On this basis, the patient in our cohort who developed seizures was at increased risk. This study excluded patients with bacterial meningitis, due to this population being at risk for seizures. In addition, our hospital guidelines (MNGHA, 2012) do not advocate the use of IC in those at increased risk of seizures and in patients with poor renal function. Our study, in agreement with Hoffman et al. Hoffman et al. (2009) did not show significant differences in ADEs associated with IC or MEM.

The number of physician and nursing visits were significantly higher in the IC group than the MEM group. This was attributed to more CCU days in the IC group, which necessitated more physician and nursing visits. As expected, the mean pharmacists' time (in min) was significantly higher in the IC group compared to the MEM group. The institute prepares both antibiotics in the intravenous admixture room. IC was given 4 times daily while MEM was given 3 times daily. The delivery by the pharmacy aide showed more delivery time with IC compared to MEM. For the same reason, more administration sets and minibags were required for the IC group. The results clearly demonstrate that significantly more time is required per day to prepare IC compared with MEM. Overall, more hospital resources are required in the preparation, dispensing and administration of IC compared to MEM.

Total hospital days, especially the total CCU days, in the IC group were significantly higher. The longer CCU days were believed to influence costing, especially in the IC group. Patients varied significantly in regard to the number of CCU days. Independent sample *t*-tests showed no significant difference in terms of mean daily hospital costs and step-down costs. However the GW costs in the IC group was significantly lower in the IC group compared to MEM ($p = 0.016$). Although total CCU costs were higher, cost per day was not statistically different between the two groups, except in terms of the GW days. More patients in the MEM group spent a greater number of days in the GW unit, which drove up mean costs in this group.

The mean total daily costs of vials in the IC group were much lower than in the MEM group (SAR 250.63 vs. 393.48). This was expected, as the cost of IC, given 4 times daily, would result in daily costs of SAR 281.60 versus MEM, given 3 times daily, at SAR 453.78. The mean costs in our study were mean costs reflecting dose changes as well. In the institution, a previous unpublished study showed that this difference in acquisition costs could result in a savings of more than SAR 2 million riyals per year, if IC was used instead of MEM. This makes IC an attractive choice as a carbapenem in patients with moderate to severe infections. Despite significant differences in acquisition costs, laboratory culture costs, pharmacist and pharmacy aide costs, the total average costs per day was not significantly different between the 2 groups (SAR 4784.46 IC and SAR 4390.13 MEM, $p = 0.370$).

It must be pointed out that some resource costs are unique to the local perspective. These include resource costs that are fixed in the institution and not related to the number of patient visits. Nursing services costs have daily rates rather than cost per visit. IC requires more frequent administration and costs were expected to be higher. However, with fixed costs, this was not apparent. Other costs such as consumables were also fixed. Most resources were variable and based on the number of patient days or related to the frequency of administration.

A one-way sensitivity analysis showed that the mean total costs were sensitive to hospital days, laboratory tests and consultations charges. These findings did not support our hypothesis that acquisition costs and costs related to administration times play a major role in total daily costs. Our study shows that costs related to the LOAS and consultation charges may affect total costs much more than acquisition costs or ADE costs.

A threshold analysis was performed on the hospital days, acquisition costs and personnel costs. The only parameter found to change the conclusion was CCU days. If the CCU value was less than SAR 33.27, average total costs of IC would be less costly than MEM. Our conclusion did not change for the rest of the parameters even if the parameter value was set to SAR 0.

This study was not without limitations. It was a retrospective single-cohort study that reflected the practices of a single institution. Although a census approach over a calendar year was used, the sample size was small.

Despite these limitations, our study has provided insight into the factors influencing hospital budgets at our institution.

7. Conclusions

This retrospective review found that although acquisition costs for IC are significantly less than those for MEM, the mean total costs per day associated with these competing carbapenems were not significantly different. The results underlined the fact that medicine acquisition costs are only a small component of the overall costs of managing moderate to severe infections. The study showed that those factors with the greatest impact on hospital costs were related to the hospital stay, especially

CCU days. Mean total costs were also sensitive to consultant visits and laboratory cultures associated with CCU admission. Nonetheless, this study supports the PTC recommendation of carbapenem selection by restricting MEM to infection control physician only. This position remains rational, and would simplify procurement and clinical practice.

8. Notes

These data were previously presented in a Master of Pharmacy mini-dissertation submitted to the University of KwaZulu–Natal. They were also presented at the 5th King Abdullah International Research Center Annual Scientific Forum in 2014.

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References

Al Aqeel, S.A., Al-Sultan, M., 2012. The use of pharmacoeconomic evidence to support formulary decision making in Saudi Arabia: methodological recommendations. Saudi Pharm. J. 20 (3), 187–194.

Anonymous, 2013. Saudi Food and Drug Administration Human Drug List. Available from: <http://old.sfda.gov.sa/NR/rdonlyres/7C3A3046-81BA-41CD-B81B-F3D3AF1D28A6/0/Human_Drug_List_Dec_2012_V1_Web.xls>.

Attanasio, E., Russo, P., Carunchio, G., Basoli, A., Caprino, L., 2000. Cost-effectiveness study of imipenem/cilastatin versus meropenem in intra-abdominal infections (structured abstract). Digest. Surg. 17 (2), 164–172 (Available from: <http://onlinelibrary.wiley.com/o/cochrane/cleed/articles/NHSEED-22000000877/frame.html>).

Badia, X., Brosa, M., Tellado, J.M., 1999. Evidence-based medicine, health costs and treatment of intra-abdominal infection. Enferm. Infecc. Microbiol. Clin. 17 (Suppl 2), 86–94.

Baldwin, C.M., Lyseng-Williamson, K.A., Keam, S.J., 2008. Meropenem: a review of its use in the treatment of serious bacterial infections. Drugs 68 (6), 803–838.

Beketov, A.S., Sidorenko, S.V., Pisarev, V.V., Komarov, R.M., 2003. Comparative clinical and epidemiological evaluation of beta-lactam antibiotics in the treatment of intraabdominal infections. Antibiot. Khimioter. 48 (3), 34–41.

Colardyn, F., Faulkner, K.L., 1996. Intravenous meropenem versus imipenem/cilastatin in the treatment of serious bacterial infections in hospitalized patients. Meropenem serious infection study group. J. Antimicrob. Chemother. 38 (3), 523–537.

Cox, C.E., Holloway, W.J., Geckler, R.W., 1995. A multicenter comparative study of meropenem and imipenem/cilastatin in the treatment of complicated urinary tract infections in hospitalized patients. Clin. Infect. Dis. 21 (1), 86–92.

Dakin, H., Wordsworth, S., 2013. Cost-minimisation analysis versus cost-effectiveness analysis, revisited. Health Econ. 22 (1), 22–34.

Drummond, M., 2006. Pharmacoeconomics: friend or foe? Ann. Rheum. Dis. 65 (Suppl 3), iii44–iii47.

Edwards, S.J., Campbell, H.E., Plumb, J.M., 2006. Cost-utility analysis comparing meropenem with imipenem plus cilastatin in the treatment of severe infections in intensive care. Eur. J. Health Econ. 7 (1), 72–78.

Embil, J.M., Soto, N.E., Melnick, D.A., 2006. A post hoc subgroup analysis of meropenem versus imipenem/cilastatin in a multicenter, double-blind, randomized study of complicated skin and skin–structure infections in patients with diabetes mellitus. Clin. Therap. 28 (8), 1164–1174 (Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/285/CN-00572285/frame.html>).

Fabian, T.C., File Jr., T.M., Embil, J.M., Krige, J.E.J., Klein, S., Rose, A., et al, 2005. Meropenem versus imipenem-cilastatin for the treatment of hospitalized patients with complicated skin and skin structure infections: results of multicenter, randomized, double-blind comparative study. Surg. Infect. 6 (3), 269–282 (Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/667/CN-00557667/frame.html>).

Geroulanos, S.J., 1995. Meropenem versus imipenem/cilastatin in intra-abdominal infections requiring surgery. Meropenem study group. J. Antimicrob. Chemother 36 (Suppl A), 191–205.

Hoffman, J., Trimble, J., Brophy, G.M., 2009. Safety of imipenem/cilastatin in neurocritical care patients. Neurocrit. Care 10 (3), 403–407.

Hou, F., Li, J., Wu, G., Zheng, B., Chen, Y., Gu, J., et al, 2002. A randomized, controlled clinical trial on meropenem versus imipenem/cilastatin for the treatment of bacterial infections. Chin. Med. J. 115 (12), 1849–1854 (Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/914/CN-00422914/frame.html>).

Kuo, B.I., Fung, C.P., Liu, C.Y., 2000. Meropenem versus imipenem/cilastatin in the treatment of sepsis in Chinese patients. Zhonghua yi xue za zhi = Chin. Med. J.; Free China Ed. 63 (5), 361–367 (Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/599/CN-00297599/frame.html>).

Merrem, 2006. [Package Insert]. AstraZeneca, North Carolina, USA.

MNGHA, 2012. King Abdulaziz Medical City Antimicrobial Guidelines Department of Infection Control, pp. 11–12.

Mohr 3rd., J.F., 2008. Update on the efficacy and tolerability of meropenem in the treatment of serious bacterial infections. Clin. Infect. Dis. 47 (Suppl 1), S41–S51.

Newby, D., Hill, S., 2003. Use of pharmacoeconomics in prescribing research. Part 2: Cost-minimization analysis – when are two therapies equal? J. Clin. Pharm. Ther. 28 (2), 145–150.

Nichols, R.L., Smith, J.W., Geckler, R.W., Wilson, S.E., 1995. Meropenem versus imipenem/cilastatin in the treatment of hospitalized patients with skin and soft tissue infections. South. Med. J. 88 (4), 397–404.

Papp-Wallace, K.M., Endimiani, A., Taracila, M.A., Bonomo, R.A., 2011. Carbapenems: past, present, and future. Antimicrob. Agents Chemother. 55 (11), 4943–4960.

Primaxin, 2006. [Package Insert]. Merck & Co., Inc., NJ, USA.

Saggabi, A. (Ed.), 2012. Pros and Cons of Pricing and Reimbursement. In: 17th International Annual ISPOR Meeting held in, June 2012, Washington DC.

Singh, J., 2013. Critical appraisal skills programme. J. Pharm. Pharmacoth. 4 (1), 76.

Song, Y.M., Zhao, J.J., Sun, L., 2001. Clinical study on meropenem and imipenem/cilastatin in treatment of respiratory tract infections. Chin. Pharm. J. 36 (2), 128 (Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/617/CN-00366617/frame.html>).

Verwaest, C., 2000. Meropenem versus imipenem/cilastatin as empirical monotherapy for serious bacterial infections in the intensive care unit. Clin. Microbiol. Infect.: Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Diseases 6 (6), 294–302 (Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/737/CN-00346737/frame.html>).

Walley, T., Haycox, A., 1997. Pharmacoeconomics: basic concepts and terminology. Br. J. Clin. Pharmacol. 43 (4), 343–348.

Xiao, H., Cao, B., He, H., Yin, C., 2010. A meta-analysis of the efficacy and safety of meropenem and imipenem in the treatment of moderate or severe pulmonary infections (provisional abstract). Chin. J. Infect. Chemother. 10 (4), 264–269 (Available from: <http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12010006026/frame.html>).

Xiao-Ju, L., Nan, X., Jia, M., Li, Z., De-Rong, L., Dun-Gong, Q., et al, 2001. A randomized controlled trial on meropenem versus imipenem/cilastatin in the treatment of bacterial infection. Chin. J. Antibio. 26 (2), 118–122 (Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/384/CN-00366384/frame.html>).

Zanetti, G., Harbarth, S.J., Trampuz, A., Ganeo, M., Mosimann, F., Chautemps, R., et al, 1999. Meropenem (1.5 g/day) is as effective as imipenem/cilastatin (2 g/day) for the treatment of moderately severe intra-abdominal infections. Int. J. Antimicrob. Agents 11 (2), 107–113.

Zhanel, G.G., Simor, A.E., Vercaigne, L., Mandell, L., 1998. Imipenem and meropenem: comparison of in vitro activity, pharmacokinetics, clinical trials and adverse effects. Can. J. Infect. Dis. 9 (4), 215–228.