Association of ertapenem and antipseudomonal carbapenem usage and carbapenem resistance in *Pseudomonas aeruginosa* among 12 hospitals in Queensland, Australia

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Objectives: The objective of this study was to determine the association between ertapenem and antipseudomonal carbapenem use and carbapenem resistance in *Pseudomonas aeruginosa* in 12 hospitals in Queensland, Australia.

Methods: Data on usage of ertapenem and other antipseudomonal carbapenems, measured in defined daily doses per 1000 occupied bed-days, were collated using statewide pharmacy dispensing and distribution software from January 2007 until June 2011. The prevalence of unique carbapenem-resistant *P. aeruginosa* isolates derived from statewide laboratory information systems was collected for the same time period. Mixed-effects models were used to determine any relationship between ertapenem and antipseudomonal carbapenem usage and carbapenem resistance among *P. aeruginosa* isolates in the 12 hospitals analysed.

Results: No relationship between ertapenem usage and *P. aeruginosa* carbapenem resistance was observed. The introduction of ertapenem did not replace antipseudomonal carbapenem prescribing to any significant extent. However, an association between greater usage of antipseudomonal carbapenems and greater *P. aeruginosa* carbapenem resistance was demonstrated.

Conclusions: It is likely that the only mechanism by which ertapenem can improve *P. aeruginosa* resistance patterns is by being used as a substitute for, rather than in addition to, antipseudomonal carbapenems.

Keywords: antimicrobial resistance epidemiology, quasi-experimental studies, statistical models

Introduction

Ertapenem is a broad-spectrum carbapenem agent that lacks activity against *Pseudomonas aeruginosa* and has been available in Australia since 2002.1 Given the increasing prevalence of extended-spectrum β-lactamase (ESBL)-producing organisms and AmpC-producing Gram-negative bacteria, the use of carbapenems to treat non-*P. aeruginosa* infections is increasing.2 The use of the antipseudomonal carbapenems (aPCs), meropenem, doripenem and imipenem, in this situation may place ecological pressure on *P. aeruginosa* isolates to develop carbapenem resistance. On the other hand, utilizing ertapenem as a ‘pseudomonal-sparing’ carbapenem agent may reduce this pressure. Furthermore, ertapenem, being highly protein bound, has a longer half-life (4 h), allowing for once-daily dosing and subsequent cost savings.3

However, there is concern that the increased use of ertapenem could in fact lead to increased rates of carbapenem resistance in *P. aeruginosa* despite its lack of clinically useful antipseudomonal activity. It has been demonstrated that ertapenem can select for aPC-resistant mutants4 although the concentrations required to select for these mutants appear to be higher than those clinically achievable using conventional dosing schedules.

Clinical studies investigating the association of ertapenem usage with carbapenem-resistant *P. aeruginosa* have adopted different methods and yielded different outcomes. One study from a single US facility failed to demonstrate any association between the introduction of ertapenem and changes in the rates of *P. aeruginosa* resistant to imipenem over 5 years.5 Another study from a single US hospital demonstrated reduced imipenem resistance to *P. aeruginosa* after the introduction of...
ertapenem. However, the improved susceptibility was related to a reduction in imipenem usage. Recently, the resistance patterns across a group of 25 randomly selected hospitals in the USA also failed to demonstrate any association between ertapenem usage and a change in aPC susceptibility rates. The hypothesis of this study is 2-fold: firstly, that the introduction of ertapenem may replace aPC prescribing for non-pseudomonal infection and subsequently reduce ecological selection pressure for \textit{P. aeruginosa}; and, secondly, that the use of ertapenem may lead to higher rates of carbapenem resistance in \textit{P. aeruginosa} as \textit{in vitro} work has demonstrated that ertapenem can select for carbapenem-resistant mutants.

**Methods**

**Setting and data collection**

Queensland is the third most populous state in Australia with a population of 4.5 million people as of June 2010. Queensland’s healthcare network consists of several tertiary referral hospitals as well as many secondary referring and regional hospitals.

Data on all \textit{P. aeruginosa} isolates isolated from January 2007 to June 2011 and their susceptibility to meropenem, were extracted from the statewide laboratory information system. Identification and antimicrobial susceptibility testing were performed using standard methods. Duplicate samples were removed, with only one phenotype per patient included. Twelve hospitals reporting more than 15 isolates per month were included in the analysis. Each isolate was dichotomized as susceptible or resistant to meropenem according to CLSI criteria. Antimicrobial usage data for ertapenem and the aPCs (meropenem, doripenem and imipenem) for the 12 hospitals were collected over the same time period for each individual hospital utilizing the statewide pharmacy dispensing and distribution software and converted into defined daily doses (DDDs) per 1000 occupied bed days (OBDs). Ertapenem usage was categorized into minor use (<2 DDDs/1000 OBDs per quarter), moderate use (2–10 DDDs/1000 OBDs per quarter) and high use (>10 DDDs/1000 OBDs per quarter). aPC usage was also categorized into minor use (<20 DDDs/1000 OBDs per quarter), moderate use (20–40 DDDs/1000 OBDs per quarter) and high use (>40 DDDs/1000 OBDs per quarter).

**Statistical analysis**

All statistical analysis was conducted using Stata 11.2 (StataCorp, College Station, TX, USA). Data were collated into quarters to minimize the effect of large monthly fluctuations in drug usage. Standard statistical methods and models are potentially inappropriate when analysing clustered or longitudinal data as within-cluster data are often correlated compared with between-cluster data, and assumptions, such as non-independence between observations, are violated. As a result, a hospital-specific mixed-effects model was employed where the serial correlation was explicitly modelled.

Previously, studies have identified a delay in the effect of antimicrobial consumption on resistance patterns and, hence, a statistical model incorporating the previous quarter’s antimicrobial usage as explanatory variables (lagged model) was investigated.

**Results**

The 12 hospitals included varied in size from 163 beds to 1008 beds (median 370 beds). A total of 20761 unique \textit{P. aeruginosa} isolates reported from January 2007 to June 2011 were included in the analysis. Over this time period, an average of 4% of isolates were identified as resistant to meropenem (Figure 1). The percentage of isolates resistant to meropenem varied between the hospitals, but in most cases was similar, the exception being Hospital H (which manages a large cystic fibrosis cohort). The mixed-effects logistic regression showed no significant change in resistance patterns over time ($P=0.9$).

Hospital G had the highest consumption of ertapenem (292 DDDs/1000 OBDs) for the study period. Hospitals A, B and L used the least, with fewer than 10 DDDs/1000 OBDs. Hospital H had the highest usage of aPCs owing to its large cohort of cystic fibrosis patients.

**Ertapenem replacing aPCs**

A mixed-effects model using uncategorized antimicrobial usage data was utilized to determine whether usage of ertapenem was replacing that of aPCs. For every increase in ertapenem usage of 1 DDD/1000 OBDs there was a corresponding decrease in aPC usage of 0.18 DDDs/1000 OBDs; however, this finding was not statistically significant ($P=0.33$). This would indicate that ertapenem prescribing was not replacing aPC prescribing to any significant extent.

**Current quarter’s antimicrobial usage (current model)**

There was a 45% (95% CI 1%–107%; $P=0.04$) increase in the odds of an isolate being resistant to meropenem if the current quarter’s aPC usage was high compared with low within the same hospital (Table 1). The consumption of ertapenem across the hospitals showed no relationship with the resistance patterns.

**Previous quarter’s antimicrobial usage (lagged model)**

The lagged model in which the previous quarter’s antimicrobial consumption was used to explain the changes in resistance patterns gave similar results. Again, the only covariate that demonstrated a significant association was high use of aPCs (>40 DDDs/1000 OBDs per quarter). The consumption of ertapenem across the hospitals showed no relationship with the resistance patterns. The lagged model is preferred to the current model for several reasons. Firstly, in the case of a multivariate regression including both the current and the previous quarter’s antimicrobial usage, only the previous quarter’s high-level aPC usage remained significant. Secondly, the diagnostics of the mixed-effects model were preferred in the lagged model, indicating a better fit for the data. Finally, the model is biologically plausible, and lags in antimicrobial resistance patterns after changes in antimicrobial usage have been well documented in the literature.

**Discussion**

This study demonstrated an association between high use of aPCs (>40 DDDs/1000 OBDs per quarter) and increased rates of resistance among \textit{P. aeruginosa} isolates, but failed to demonstrate any association between consumption of ertapenem and patterns of resistance to meropenem among \textit{P. aeruginosa}. This is similar to the results obtained in previous studies and adds further weight to the hypothesis that, although...
Ertapenem can select for cross-resistant mutants, the concentrations required are much higher than achievable by standard dosing. This study indicated that the majority of ertapenem prescribing was additional to, rather than a replacement for, aPC prescribing. It is likely that the only mechanism by which ertapenem may improve resistance patterns is by being used as a substitute for, not in addition to, aPC usage.

There are limitations to the study, including the retrospective design and potential bias, including confounding, that may have been introduced. For example, hospitals are complex entities with many factors at play, including case-mix, and not all these factors can be measured and adjusted for. The low baseline *Pseudomonas* resistance rates throughout the state of Queensland (~4%) compared with those reported in other studies, which have been as high as 25%, make demonstrating a reduction difficult.

The strengths of the study include the high-quality antimicrobial usage data, which are based upon dispensing and distribution reports obtained from a single pharmacy software program used throughout the state. This is unusual as many studies obtain the data from pharmacy purchasing records, and these may not correlate well with actual consumption. Additional strengths include the multicentre design of the study and the robust statistical methods, which are appropriate for complex clustered data. The mixed-effects statistical model used allows for a random intercept and slope for each hospital to account for differing levels of resistance and changes among the 12 hospitals during the study period.

The most commonly used aPC, meropenem, is due to come off patent soon, and a large price drop could see a dramatic increase in use. If there is no longer a financial incentive to prescribe ertapenem it is important that further resistance monitoring takes place to see if this dynamic relationship develops.

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**Table 1. Summary of mixed-effects model**

<table>
<thead>
<tr>
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<th>Mixed-effects model utilizing current quarter’s antimicrobial usage</th>
<th>Mixed-effects model utilizing previous quarter’s antimicrobial usage</th>
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<tr>
<td></td>
<td>OR</td>
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<td>0.97–1.02</td>
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**Figure 1.** Ertapenem (dashed lines) and aPC (dotted lines) usage in DDDS/1000 OBDs and the percentage of meropenem-resistant *P. aeruginosa* isolates (continuous lines) for each of the 12 hospitals analysed. q1, first quarter.
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References