Original Article

Estimation of the Probability to Target Attainment to the Pharmacokinetic/ Pharmacodynamic Index of Ertapenem in Elderly Inpatients

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ABSTRACT

Background: Infectious diseases are one of the most causes of hospitalization and death in adults in the elderly and this population is prone to develop complications and pharmacokinetic/pharmacodynamic changes. **Objectives:** To estimate the probability to target attainment (PTA) to the pharmacokinetic/pharmacodynamic (PK/PD) index of ertapenem for older adults hospitalized in a medical ward. **Materials and Methods:** In a prospective and observational analysis, free drug concentrations of ertapenem were determined in older adults hospitalized at medical ward setting and compared with EUCAST epidemiological cut-off values (ECOFF: 0.064 mg/L) to extreme MIC (64 mg/L), using 1000 Monte Carlo simulations to estimate therapeutic target attainment (%f T ≥ MIC ≥ 40%). **Results:** Five elderly inpatients with renal impairment and hypoalbuminemia were included with eight samples per patient (n = 40 observations). Monte Carlo simulations shown free ertapenem concentrations attain to PK/PD index on the MIC interval from 0.064 to 4 mg/L. **Conclusion:** If pathogen MICs are ≥ 4 mg/L, elderly inpatients could not attain to the PK/PD target of ertapenem in medical ward setting, rising probability of antimicrobial resistance and therapeutic failure in this population.

Key words: Elderly, Ertapenem, Pharmacokinetics, Probability to target attainment, PK/PD index.

INTRODUCTION

Infectious diseases are one of the most causes of hospitalization and death in adults in the elderly.[1]

Moreover, this population is prone to develop complications during hospital stay due to frailty.[2] This vulnerability occurs due to physiological changes and immunosenescence, increasing the risk and severity of infections in older adults, respectively. Additionally, classical signs and symptoms in younger adults such as fever or elevated white blood cells are often unlikely clinical features in the elderly.[3]

To the other hand, antibiotic recommendations for hospitalized patient are divided by medical ward or intensive care unit and the selection of the agent to treat empirically is based in likely pathogens, epidemiologic factors, clinical efficacy, risk factors for antimicrobial resistance and comorbidities.[4]

One of the antimicrobial empirical alternatives in the medical ward setting is ertapenem, a carbapenem agent with broad spectrum against gram-positive and gram-negative aerobic and anaerobic bacteria, frequently used for the treatment of community acquired or nosocomial infections, including extended spectrum beta lactamase (ESBL), but restricted activity against *Pseudomonas aeruginosa*, *Acinetobacter spp*, methicillin-resistant *Staphylococci* and *Enterococci*. Chemically, is the only 1-beta methyl carbapenem agent, conferring it

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clinical and toxicological differences compared to others carbapenem (as imipenem or meropenem).[5]

Usually, 1 g of ertapenem once a day is effective as monotherapy for community acquired pneumonia requiring hospitalization, acute pelvic infections, complicated urinary, intra-abdominal and skin and/or subcutaneous tissue infections.[6]

Moreover, one of its therapeutic advantages is the administration as a once-a-day treatment, due to its pharmacokinetic properties: highly bonded to albumin (> 90%) with the longer elimination half-life in the carbapenem group. It is excreted predominantly by urine (80% as total drug, 38% as unaltered drug), with a half-life varying from 4 hrs in young adult volunteers, up to 14 hr in patients with end-stage renal disease (CrCl <15 mL/min).[6] Nevertheless, dosing adjustments by age, gender, weight or liver disease are not recommended based in individual pharmacokinetic studies in elderly subjects.

As a bactericidal agent, the most important pharmacokinetic/pharmacodynamic index predicting *in vivo* efficacy of ertapenem is the time that the free (or unbound) drug concentration is maintained above the minimum inhibitory concentration ($fT \geq MIC$) of the pathogen, in at least 40% of the administration interval.[7]

Unfortunately, frail elderly inpatients can suffer physiological changes related to aging. For instance, glomerulosclerosis that reduces 1 mL/min in glomerular filtration rate (GFR) per year after 40 years old.[8] Moreover, creatinine production, derived from muscular metabolism and degradation is affected due to progressive muscle loss.[9] Body composition is considered a frailty marker for older adults and is affected by aging, reduced "hydrophilic compartment" (muscle, bone and water) and enhanced fat mass relative to muscle loss (lipophilic compartment), altering drug disposition.[10] Plasmatic albumin reducing it's exacerbated by chronic diseases (e.g. renal disease), producing hypoalbuminemia and affecting unbound fraction of drugs highly bound to albumin, as ertapenem.[11]

However, the physiological changes associated with aging can alter the drug disposition affecting the attainment of the pharmacokinetic/pharmacodynamic (PK/PD) target and common clinical conditions as hypoalbuminemia and renal impairment are likely in frail elderly inpatient.

The aim of the study was to estimate probability to target attainment (PTA) to the PK/PD index of ertapenem in elderly inpatients in a medical ward setting.

MATERIALS AND METHODS

This prospective and observational study was carried out in elderly inpatients admitted to medical ward with infectious disease, treated with ertapenem 1 g given by intermittent infusion of 30 min and were recruited between December 2015 and October 2017. The exclusion criteria were patients in hemodialysis or peritoneal dialysis and who were unable to give informed consent. Ethical and Scientific Committee at Clinical Hospital´s Universidad of Chile approved the study protocol to ensure Good Clinical Practices and the compliance of legal issues. Age, actual weight, plasmatic albumin and serum creatinine were recorded as variables related to physiological changes of aging. Renal function was estimated by Cockcroft-Gault formula. All results were expressed in mean ± standard deviation.

The PK/PD index for the second ertapenem dose or later was estimated for each of microbiological inhibition concentration (MIC) breakpoint obtained from EUCAST (European Committee on Antimicrobial Susceptibility Testing) epidemiological cut-off values (ECOFF: 0.064 mg/L) and the extreme MIC (64 mg/L) of *Klebsiella pneumoniae* (KP). Software MATLAB® and the application SimBiology were used to perform PK/PD analysis and for the population model building (data not shown). Monte Carlo approximation was carried out to simulate 1000 iterations approximation with a confidence interval of 95%.

The PTA percentages were tabulated in a spreadsheet in Microsoft Excel®, contrasted to MICs obtained from EUCAST and plotted to estimate the breakpoints using Software GraphPad Prism 8®.

RESULTS AND DISCUSSION

Five older adults (79.0 ± 6.8 years; 3 women and 2 men) were treated with ertapenem with moderate renal impairment (ClCr 44.3 ± 16.5 mL/min) and hypoalbuminemia (2.9 ± 0.4 g/dL). Patients were selected for sampling (8 per patient; n=40 observations) and the data was collected and for estimation of attainment to the PK/PD index by stochastic approximation. In this condition, by Monte Carlo simulation, 1000 elderly inpatients treated with 1 g of ertapenem against KP nosocomial infection with a MIC of 4 mg/L or less, could free ertapenem concentration be above the MIC until 40% of the administration interval in a day (9.6 hr) (Figure 1).

Probability of target attainment for %fT>MIC in 1000 simulations for ertapenem 1 g/day administration versus MIC value of *K. pneumoniae* obtained from

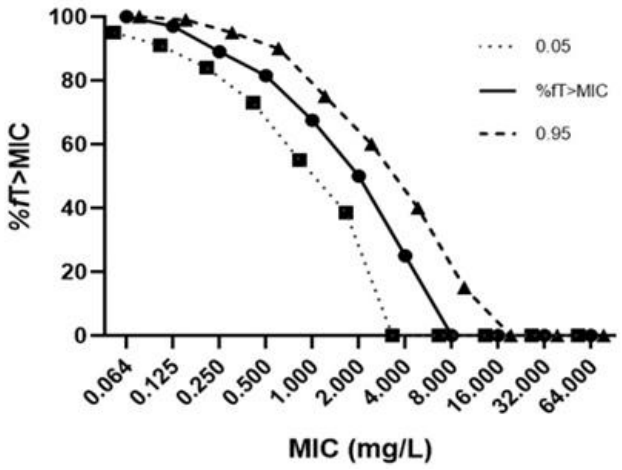

Figure 1: Probability of target attainment (fT ≥ MIC ≥ 40%) with 1 g ertapenem dosing for older adults hospitalized at medical ward with a confidence interval of 95%.

EUCAST (black continuous line: mean values; pointed discontinuous line: 5th percentile; discontinuous line: 95th percentile).

It is important to emphasize that the goals of PK/PD index for patients hospitalized in the medical ward are different for who are hospitalized in the Intensive Care Unit, needing to attain 100% to the PK/PD index to reduce intra-treatment resistance rates.[12]

In the present study, a MIC ≥ 4 mg/L could not attain to the PK/PD index of ertapenem in elderly inpatients, similarly to *in vitro* tests shown susceptible pathogens are inhibited to concentration of < 4 mg/L.6

Moreover, estimation of PTA is relevant for determining clinical success and reduction of resistance rate in a population poorly represented in clinical trials.[13] This is the first research carried out only with hospitalized older adults in a medical ward setting, developing and teaching a clinical pharmacy activity of therapeutic drug monitoring in a special population.

CONCLUSION

In elderly patients hospitalized in a medical ward setting, if pathogen MICs are ≥ 4 mg/L, they could not attain to the PK/PD target of ertapenem, rising probability of antimicrobial resistance and therapeutic failure in this population.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ClCr: Creatinine Clearance; **ECOFF:** Epidemiological cut-off value; **EUCAST:** European Committee on Antimicrobial Susceptibility Testing; **KP:** *Klebsiella pneumoniae*; **MIC:** Minimum inhibitory concentration; **PK/PD:** Pharmacokinetic/pharmacodynamic; **PTA:** Probability to target attainment.

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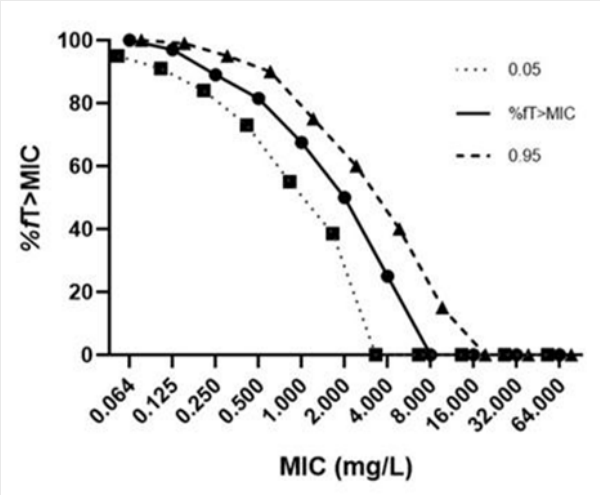
PICTORIAL ABSTRACT



SUMMARY

Ertapenem is a time-dependent antibacterial agent highly bonded to albumin, predominantly excreted by via renal and administered as a once daily treatment, it conferring advantages in antimicrobial selection. Nevertheless, pathophysiological changes, such as renal failure and hypoalbuminemia, may alter pharmacological properties, changing safety and effectiveness profile in the elderly. Indeed, if MIC is ≥ 4 mg/L against KP infection, treatment could not attain to the optimal PK/PD index of bactericidal effect.

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