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Short Communication

Pharmacokinetics of imipenem in critically ill patients during empirical treatment of nosocomial pneumonia: A comparison of 0.5-h and 3-h infusions☆

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ABSTRACT

In critically ill patients, pathophysiological changes alter the pharmacokinetics of antibiotics. Imipenem exhibits primarily time-dependent killing. Its administration by prolonged infusion may increase the time for which its plasma concentration exceeds the minimum inhibitory concentrations (MICs) of suspected pathogens. The objectives of this study were to compare the pharmacokinetic parameters of imipenem administered by standard short infusion (1 g imipenem/1 g cilastatin over 30 min three times daily) and by extended infusion with a reduced total dose (0.5 g imipenem/0.5 g cilastatin over 3 h four times daily) and to compare the target pharmacokinetic/pharmacodynamic indices, namely percentage of the dosing interval for which the free plasma concentration of imipenem exceeds the MIC and 4× MIC ($\%fT_{>MIC}$ and $\%fT_{>4\times MIC}$) of 0.5, 1, 2 and 4 mg/L, for these two regimens in critically ill adult patients with nosocomial pneumonia on Day 2 of empirical antibiotic therapy. The study included 22 patients. Whilst no significant differences were found between both groups for $\%fT_{>MIC}$, $\%fT_{>4\times MIC}$ was 87.4 ± 12.19%, 68.6 ± 15.08%, 47.31 ± 6.64% and 27.81 ± 9.52% of the 8-h interval in the short infusion group for MICs of 0.5, 1, 2 and 4 mg/L, respectively, and 85.15 ± 17.57%, 53.14 ± 27.27%, 13.55 ± 24.47% and 0 ± 0% of the 6-h interval for the extended infusion group. In conclusion, administration of 0.5 g of imipenem by a 3-h infusion every 6 h does not provide sufficient drug concentrations to treat infections caused by pathogens with a MIC of ≥2 mg/L.

1. Introduction

Hospital-acquired pneumonia (HAP) is the second most common hospital-acquired infection, leading to the greatest number of nosocomial infection-related deaths [1]. Besides other factors, early and adequate antibiotic treatment has a major prognostic impact and is therefore of particular clinical relevance [2]. Timely initiation of antibiotic therapy must be coupled with adequate dosing to ensure rapid attainment of effective antibiotic concentrations at the site of infection [3].

In critically ill patients, pathophysiological changes (fluid shift phenomenon due to damage to the vascular endothelium resulting in fluid leak, or altered renal clearance) may affect the pharmacokinetics of antibiotics [4]. Thus, appropriate dosing modifications should be applied to prevent inadequate antibiotic concentrations and subsequent therapeutic failure [5].

Imipenem, a carbapenem antibacterial agent, exhibits primarily time-dependent killing. As with other β-lactams, an important pharmacokinetic/pharmacodynamic (PK/PD) index that correlates with its therapeutic efficacy is the time for which its free plasma concentration is above the minimum inhibitory concentration (MIC) of a pathogen ($fT_{>MIC}$) [6].

According to the manufacturer's information, imipenem solution is sufficiently stable for 4 h at 15–25 °C [7]. Administration by prolonged infusion may offer an opportunity to increase $fT_{>MIC}$ within these limitations of stability at room temperature.

☆ The results of this study were partially presented as a poster at the 11th Conference of the European Association for Clinical Pharmacology and Therapeutics, 28–31 August 2013, Geneva, Switzerland [PP 198].

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A prospective randomised study was conducted to compare the pharmacokinetics of imipenem administered by two different dosing strategies in a cohort of critically ill patients with HAP. Since even larger studies have not demonstrated a clear impact of prolonged infusion on clinical outcome [8], we aimed to show whether lower doses of imipenem administered by prolonged infusion could provide PK profiles comparable with those observed after short infusion of a standard dosage.

2. Materials and methods

2.1. Patients

This single-centre, randomised, open-label, comparative study was performed in a 20-bed general intensive care unit (ICU) in General University Hospital (Prague, Czech Republic). Inclusion criteria were HAP, treatment with imipenem/cilastatin (recommended by a hospital microbiologist) and expected continuation of mechanical ventilation for ≥48 h from recruitment. HAP was defined according to US Centers for Disease Control and Prevention (CDC) criteria [9] as the presence of a new infiltrate on the chest radiograph plus two of the three following conditions: (i) core temperature >38.3 °C; (ii) blood leukocytes >10^4 cells/mL; and (iii) purulent tracheal secretion.

Patients younger than 18 years of age and those with an allergy to carbapenems, hepatic dysfunction assessed as total serum bilirubin >27 μmol/L (>1.5 mg/dL), neutropenia (<500 granulocytes/mm^3), acute or chronic renal failure assessed by serum creatinine concentrations >280 μmol/L or those requiring continuous renal replacement therapy, obese patients with a body mass index (BMI) >35 kg/m^2 or weight >110 kg, and pregnant women were excluded.

Baseline demographic, biochemical and clinical data were recorded for each patient at the time of enrolment. The DuBois & DuBois formula was used to calculate body surface area (BSA) [10].

2.2. Study design

Patients meeting established criteria were randomised by the random permuted blocks method to receive either a short infusion (bolus group) or extended infusion (extended group) regimen of imipenem/cilastatin. After a period of 48 h, the antibiotic treatment was de-escalated or adjusted according to the patient's microbiology findings and a hospital microbiology consultant's recommendation. Patients in the bolus group received a dose of 1 g imipenem/1 g cilastatin over 30 min every 8 h. The total dose administered to each patient during the study period of 48 h was 6 g imipenem/6 g cilastatin. Patients in the extended group received an initial loading dose of 1 g imipenem/1 g cilastatin over 30 min followed by an infusion of 0.5 g imipenem/0.5 g cilastatin administered over 3 h every 6 h. The total dose per patient in this group was 4.5 g imipenem/4.5 g cilastatin during 48 h.

Imipenem/cilastatin (Tienam®) (Merck Sharp & Dohme B.V., Haarlem, The Netherlands) was used in the study. In both groups, each dose of antibiotic was reconstituted in 100 mL of sterile 0.9% sodium chloride solution immediately before administration and was infused by a separate lumen of a central venous catheter using an automatic high-precision infusion pump (B. Braun, Melsungen, Germany).

2.3. Blood sampling

On the second day of imipenem treatment, blood samples for determination of imipenem concentrations were obtained from a multipurpose arterial catheter, used in each subject during their whole ICU stay, at the following times: immediately prior to imipenem/cilastatin administration (time 0) and at 20 min, 40 min, 4 h, 6 h and 8 h after administration of the infusion in the bolus group; and at times 0, 120 min, 190 min, 4 h, 5 h and 6 h in patients in the extended group. For each sample, 2.7 mL of blood was drawn and added to a heparinised tube (BD Vacutainer® Plus plastic citrate tube; BD Diagnostics, Franklin Lakes, NJ) and was centrifuged at $1.2 \times 10^3 \times g$ for 10 min at 5 °C using a Heraeus® Biofuge® Primo R centrifuge (Thermo Fisher Scientific Inc., Waltham, MA). Subsequently, 200 μL of the resulting plasma were transferred to a 1.5 mL Eppendorf tube (Sarstedt, Nümbrecht, Germany) and an equal volume of 0.2 M MOPS [3-(*N*-morpholino)propanesulfonic acid buffer], a stabilising solution that protects the antibiotic from bacterial degradation, was added. This mixture was vortexed for 10 s and was stored at −80 °C before analysis for a maximum of 1 week.

2.4. Imipenem assay

Plasma imipenem concentrations were determined by reversed-phase high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection using the method developed by Šiller et al. [11]. First, 600 μL of acetonitrile was added to stabilised plasma for deproteinisation, the mixture was thoroughly vortexed for 15 s and was then centrifuged at $3.38 \times 10^3 \times g$ at 4 °C for 30 min using a Jouan BR4i centrifuge (Jouan Inc., Winchester, VA). Subsequently, 400 μL of the supernatant were transferred to a clean test tube and was evaporated under nitrogen at 40 °C. The residue in the test tube was dissolved in 200 μL of mobile phase A.

The analysis was performed using a Shimadzu LC20 Prominence HPLC system (Kyoto, Japan) in gradient elution mode consisting of 25 mM potassium dihydrogen phosphate/methanol (92:8, v:v), pH 6.5 (mobile phase A) and 100% methanol (mobile phase B) on a reserved-phase C_{18} LiChrospher® LiChroCART® 250-4 (Merck, Darmstadt, Germany) column. The effluent was monitored by UV detection at 313 nm. Interference with cilastatin or thienamycin was not detected. Cefuroxime (Sigma–Aldrich Chemie, Steinheim, Germany) was used for calibration as an internal standard.

The calibration curve was linear from 0.5 mg/L to 200 mg/L, with a coefficient of correlation and reliability of ≥0.9998. The limit of detection and the limit of quantification were 0.1719 mg/L and 0.2641 mg/L, respectively. The intraday precision values characterised by coefficients of variation (CV) were 12.53% (1 mg/L), 1.11% (10 mg/L) and 11.65% (100 mg/L). The interday precision values characterised by CV were 14.67% (1 mg/L), 4.91% (10 mg/L) and 9.01% (100 mg/L). Accuracy was 106.98% (1 mg/L), 99.35% (10 mg/L) and 91.53% (100 mg/L).

2.5. Statistical and pharmacokinetic analysis

The minimum (C_{min}) and maximum (C_{max}) plasma concentrations of imipenem were determined as the lowest and highest measured value in each subject. Further PK parameters, including elimination rate constant (k_{el}), elimination half-life ($t_{1/2}$), volume of distribution (V_d), area under the concentration–time curve (AUC) and total imipenem clearance (CL_{imp}), were calculated using a non-compartment model.

The target PK/PD indices, namely the percentage of the dosing interval for which the free plasma concentration of imipenem exceeds the MIC ($fT_{>MIC}$) and 4× MIC ($fT_{>4\times MIC}$), were calculated from the individual concentration–time curves for MICs of 0.5, 1, 2 and 4 mg/L. Free fractions were calculated from total concentrations using literature data on plasma binding [7]. The time–concentration curves were constructed by linear interpolation from the adjusted levels, and the time above the corresponding multiple of MIC was determined by using the trapezoid rule.