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Short Communication

Total and unbound ceftriaxone pharmacokinetics in critically ill Australian Indigenous patients with severe sepsis

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ABSTRACT

In the absence of specific data to guide optimal dosing, this study aimed to describe the pharmacokinetics of ceftriaxone in severely septic Australian Indigenous patients and to assess achievement of the pharmacodynamic target of the regimens prescribed. A pharmacokinetic study was conducted in a remote hospital intensive care unit in patients receiving ceftriaxone dosing of 1 g every 12 h (q12h). Serial blood and urine samples were collected over one dosing interval on two consecutive days. Samples were assayed using a validated chromatography method for total and unbound concentrations. Concentration–time data collected were analysed with a non-compartmental approach. A total of 100 plasma samples were collected from five subjects. Ceftriaxone clearance, volume of distribution at steady-state, elimination half-life and elimination rate constant estimates were 0.9 (0.6–1.5) L/h, 11.2 (7.6–13.4) L, 9.5 (3.2–10.2) h and 0.07 (0.07–0.21) h^{-1}, respectively. The unbound fraction of ceftriaxone ranged between 14% and 43%, with a higher unbound fraction present at higher total concentrations. The unbound concentrations at 720 min from the initiation of infusion for the first and second dosing intervals were 7.2 (4.8–10.7) mg/L and 7.8 (4.7–12.1) mg/L respectively, which exceeds the minimum inhibitory concentration of all typical target pathogens. In conclusion, the regimen of ceftriaxone 1 g q12h is adequate for critically ill Australian Indigenous patients with severe sepsis caused by non-resistant pathogens.

1. Introduction

Sepsis and severe sepsis are two of the commonest intensive care unit (ICU) admission diagnoses for the Australian Indigenous population [1,2]. Up to 60% of all hospital deaths for Indigenous patients are related to infection, 56% of which are associated with bacterial sepsis [3].

A recent systematic review documented the significant differences in antibiotic pharmacokinetics that may occur between different ethnic groups [4]. In relation to the Australian Indigenous, physiological differences that can alter antibiotic pharmacokinetics include having 30% less nephrons [4], sharing similar allele frequencies of some cytochrome P450 enzymes with the East Asian population [5], and having smaller body mass, higher central fat and thinner extremities compared with the non-Indigenous population [6].

Ceftriaxone is a third-generation cephalosporin and is a commonly used antibiotic in the ICU. It shows a time-dependent bacterial kill characteristic [7], where maximum bacterial kill effects are anticipated when the plasma free drug concentration exceeds the minimum inhibitory concentration ($fT_{>MIC}$) for ≥60–70% of the dosing interval [8]. It has mixed renal and biliary elimination, however due to its uncommon pharmacokinetic properties of high binding to serum albumin (83–95%) and a relatively long elimination half-life ($t_{1/2}$) of 6–8 h, renal impairment rarely warrants dose adjustment [9,10]. The presence of hypoalbuminaemia, like numerous other conditions that are commonly seen in the critically ill, may lead to altered plasma ceftriaxone concentrations [11]. In the absence of therapeutic drug monitoring, it can be difficult to prescribe drugs

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such as ceftriaxone with confidence for critically ill patients and know that dosing is adequate.

There are very limited data on the effect of critical illness on the disposition of ceftriaxone, especially in the Australian indigenous. Hence, this study aimed to describe the pharmacokinetics of total and unbound ceftriaxone in critically ill Australian Indigenous patients with severe sepsis.

2. Materials and methods

2.1. Setting

A prospective, observational pharmacokinetic study was conducted in the ICU of Alice Springs Hospital, a remote hospital in the Northern Territory of Australia. Ethics approval was granted from the local and university ethics committees, and written consent was obtained from all participants/next of kin.

2.2. Study population

Inclusion criteria were: (i) Australian Indigenous; (ii) ≥18 years of age; (iii) confirmed or suspected severe sepsis within the previous 48 h; (iv) clinical indication for ceftriaxone; and (v) arterial line and an indwelling urinary catheter in situ. Exclusion criteria were: (1) creatinine clearance (CL_{Cr}) <15 mL/min; (ii) requirement for haemodialysis or continuous renal replacement therapy; and (iii) pregnancy.

2.3. Study protocol

The dose and frequency of ceftriaxone (Ceftriaxone Sandoz®; Sandoz Pty Ltd., Sydney, Australia) were determined by the treating physician. Ceftriaxone was reconstituted in 100 mL of sodium chloride 0.9% and was infused intravenously via a central venous catheter over 30 min. Ten 2-mL blood samples were collected from the existing arterial line over the 12-h dosing interval at 0, 30, 60, 75, 90, 120, 180, 360, 480 and 720 min from the initiation of infusion. A second set of samples with the same regimen was obtained the next day. Urine was collected throughout the duration of both dose intervals via an indwelling catheter. Demographics, clinical information and routine laboratory test results performed on the study days were also recorded.

All plasma samples were assayed for total (unbound and bound) ceftriaxone concentration and five plasma samples for each dosing interval (30, 90, 180, 360 and 720 min from the initiation of infusion) were assayed for the unbound concentration.

2.4. Sample handling and storage

Blood and urine samples were stored at 2–8 °C immediately after collection. One millilitre of collected urine sample was pipetted into a cryovial. Within 8 h of sampling, the blood-containing sampling tubes and the urine-containing cryovials were centrifuged at 5000 rpm for 6 min. Plasma samples were then aspirated into cryovials and were batched with the urine cryovials. They were then stored at –70 °C. The total urine sample was used for creatinine assay in Alice Springs Hospital Pathology, with the measured CL_{Cr} subsequently determined. Upon completion of recruitment, plasma and urine samples were packed with dry ice and were freighted to the Burns, Trauma & Critical Care Research Centre of The University of Queensland (Brisbane, Australia) for drug assay.

2.5. Drug assay

2.5.1. Plasma samples

Total and unbound concentrations of ceftriaxone in plasma were measured by a validated ultra-high-pressure liquid chromatography–tandem mass spectroscopy (UHPLC-MS/MS) method on a Shimadzu Nexera connected to a Shimadzu 8030 + triple quadrupole mass spectrometer (Shimadzu Corp., Kyoto, Japan). Clinical samples were assayed in batches alongside calibrators and quality controls (QCs) and the results were subject to batch acceptance criteria.

The free fraction was first isolated by ultrafiltration at 37 °C with a Centrifree® Ultrafiltration Device (Merck Millipore, Tullagreen, Ireland), and the ultrafiltrated plasma was then processed as a typical plasma sample in order to obtain the unbound concentration. Ionisation was by positive mode electrospray. Detection was monitored by MRMs at m/z 554.7→396.1 (ceftriaxone) and 557.7→399.1 (d3-ceftriaxone). Linearity was validated over the concentration range 2 mg/L–200 mg/L (total) and 0.2 mg/L–200 mg/L (unbound). Precision and accuracy were within 8.4% for total analysis and 12.3% for unbound analysis at all three concentrations tested. The unbound fractions of QCs (total ceftriaxone concentration) were 8.3% (low, 3 mg/L), 9.0% (medium, 10 mg/L) and 12.6% (high, 80 mg/L). Unbound concentrations were measured with precision ($n = 6$) of 9.2% (low), 4.1% (medium) and 3.5% (high).

2.5.2. Urine samples

Concentrations of ceftriaxone in urine were measured from 10 to 10,000 mg/L by a validated high-pressure liquid chromatography–ultraviolet (HPLC-UV) method on a Shimadzu Prominence HPLC system (Shimadzu Corp.). Urine samples were filtered and diluted with water in preparation for instrumental analysis. Ceftriaxone was monitored at 304 nm and the assay method was validated for linearity, lower limit of quantification, matrix effects, and precision and accuracy using the US Food and Drug Administration (FDA) criteria for bioanalysis [12]. The precision and accuracy were within 0.9% and 7.9%, respectively.

2.6. Pharmacokinetic analysis

Data collected from plasma samples were analysed using a non-compartmental approach with the Pmetrics® software package v.1.4.2 for R® v.3.2.2. The unbound ceftriaxone samples were also contrasted with the corresponding total ceftriaxone concentrations to determine the unbound fraction of ceftriaxone (described as a percentage) at different times over the dosing interval.

2.7. Statistical analysis

Continuous data are presented as median (range) and categorical data as counts (%). The amount of ceftriaxone recovered in urine was tested for correlation with the measured CL_{Cr} data using linear regression with Microsoft® Excel for Mac (Microsoft Corp., Redmond, WA).

3. Results

Five Indigenous patients were included in this study and contributed a total of 100 blood samples. All patients received a dosing regimen of ceftriaxone 1 g every 12 h (q12h). The demographics, clinical information and pharmacokinetic parameter estimates are presented in Table 1. The concentration–time profile for the sampling occasions is shown in Fig. 1, and the unbound fraction of ceftriaxone concentration throughout the dosing interval is presented in Fig. 2, which shows a trend of a decreasing unbound fraction throughout the dosing interval that corresponds with decreasing drug concentrations. Fig. 3 describes the correlation between unbound fraction and total ceftriaxone concentration for each individual patient. In general, higher ceftriaxone concentrations were found to correspond with higher unbound fractions.

There was no clear association observed between CL_{Cr} and the amount of ceftriaxone recovered in the urine over the dose interval