A comparative analysis of pharmacokinetics of ceftriaxone in serum and pleural fluid in humans: a study of once daily administration by intramuscular and intravenous routes

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Pleural fluid and serum pharmacokinetics of ceftriaxone were performed in thirteen patients with pleural effusion. One gram of ceftriaxone was administered once daily intravenously in six patients and intramuscularly in seven patients. Ceftriaxone concentrations were measured in serum and pleural fluids in both groups on the first day of administration and in four patients of the intramuscular group on the fourth day of administration. The mean serum peak concentration at 1 h was 199 mg/L (S.E.M. 63.2) in the iv group and 80.5 mg/L (S.E.M. 12.0) in the im group. The mean serum trough concentrations in the two groups at 24 h were 27.5 mg/L (S.E.M. 12.6) and 29.7 mg/L (S.E.M. 5.2) respectively. In the pleural fluid, mean peak concentration was 20.1 mg/L (S.E.M. 4.7) at 6 h in the iv group and 15.3 mg/L (S.E.M. 5.1) at 12 h in the im group. The mean trough concentration was 9.6 mg/L (S.E.M. 1.9) and 13.3 mg/L (S.E.M. 3.1) at 24 h in the two groups respectively. On the fourth day of intramuscular administration the serum and pleural fluid peak and trough concentrations were higher when compared with the first day, consistent with a cumulative effect. The serum and pleural fluid concentrations of ceftriaxone following intravenous and intramuscular administration were well above the MIC<sub>90</sub> of most common respiratory pathogens indicating good penetration into extracellular spaces. Further, these serum and pleural fluid antibiotic concentrations could be maintained even after a single intramuscular injection of the drug, thus indicating its usefulness as a parenteral mode of therapy on a domiciliary basis with a significant cost-saving potential.

In conclusion, intramuscular administration of ceftriaxone would appear to be a convenient method of administering parenteral therapy in lower respiratory tract infections in the hospital and community, with pharmacokinetics very similar to those exhibited by the intravenous route.

Introduction

Community acquired pneumonia is a serious infection associated with a significant morbidity (Woodhead et al., 1987) and mortality (MacFarlane et al., 1982). Parapneumonic pleural effusions may occur in up to 40% of patients with bacterial pneumonia. Of these 10% will progress to develop an empyema (Light, 1990; Strange & Sahn, 1991). Early treatment of pneumonia with an appropriate antibiotic exhibiting...
adequate penetration into the pleural cavity may alleviate this progression (Bartlett, 1988).

*Streptococcus pneumoniae* and *Haemophilus influenzae* account for more than 75% of causes of bacterial pneumonia (MacFarlane, 1987) and for a majority of cases of infective exacerbation of chronic obstructive airways disease (Basran et al., 1990; Hosker, Cooke & Hawkey, 1994). Therefore any antibiotic used in the treatment of lower respiratory tract infections would have to provide adequate cover against these two organisms.

Ceftriaxone is a third generation cephalosporin antibiotic with a wide spectrum of activity against many common respiratory pathogens. It has a long half life which allows once daily administration by either the intravenous or intramuscular route. It has been shown to be effective in the treatment of bacterial pneumonia (Barradas et al., 1989; Bassetti et al., 1991) and to produce satisfactory antibiotic concentrations in pleural fluid when given once daily intravenously (Benoni et al., 1986; Scaglione, Raichi & Fraschini, 1990).

Once daily intramuscular administration offers a convenient method of administration of the drug in hospitals and in the community. It would allow early discharge from hospital with domiciliary administration of the antibiotic which could result in substantial saving in cost. Pleural fluid kinetics of ceftriaxone after intramuscular administration has not been evaluated.

The aims of this study, which was conducted on patients with proven pleural effusions, were to compare serum and pleural-fluid pharmacokinetics of ceftriaxone after intravenous and intramuscular administration and to compare plateau concentrations of the drug in serum and pleural fluid with the minimal inhibitory concentrations (*MIC*$_{50}$) for common respiratory pathogens.

**Methods**

Adult patients with pleural effusions referred to the respiratory unit for therapeutic or diagnostic pleural aspiration were eligible for inclusion into the study. Nine men and four women with a mean age of 67 years (range 44–81) were enrolled. The study was designed as an open label, prospective comparison of serum and pleural fluid kinetics of ceftriaxone following intravenous and intramuscular injection.

Patients with respiratory failure, acute renal failure, changing renal function and patients undergoing renal dialysis were excluded from the study. Those with previous (within one month) or concurrent antibiotic therapy (except ceftriaxone) were excluded. All patients provided informed consent and were non randomly assigned to the intravenous (six patients) and intramuscular (seven patients) treatment groups. The fluids of three patients were transudates while those of the remaining ten were exudates (Table I).

One gram of ceftriaxone (Hoffman-La Roche Ltd) was injected either intravenously dissolved in 10 mL of sterile water over 3 min into an antecubital vein via an indwelling cannula or was injected intramuscularly dissolved in 3.5 mL of 1% lignocaine hydrochloride BP (Astra Pharmaceuticals UK) into the gluteus maximus. Simultaneous pleural fluid and venous blood specimens were drawn from each patient 1, 3, 6, 12 and 24 h following a single injection of 1 g of ceftriaxone. Pleural fluid was obtained using repeated needle aspiration or where clinically indicated through an indwelling intercostal drain, without continuous draining, during the study period. Venous blood
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samples were collected through indwelling heparinised cannulae inserted into the contralateral arm. Venous blood specimens were centrifuged immediately and the resulting plasma and corresponding pleural fluid were stored frozen at $-20^\circ$C awaiting analysis.

In four out of seven patients receiving intramuscular ceftriaxone we had the opportunity to repeat the pharmacokinetic study in blood and pleural fluid on the fourth day of treatment. This provided an opportunity to study the cumulative effect of the drug when administered on a once daily basis.

The concentration of ceftriaxone in blood and pleural fluid were measured by an agar diffusion bioassay procedure using antibiotic medium No. 1 (Unipath CM 327). The surface of the agar was flooded with a suspension of *Providencia rettgeri* (J294) prepared from an overnight broth culture diluted to an optical density of 0.004 at 630 nm. Calibrators and internal controls were prepared from standard powder adjusted for potency (range of calibrators 4, 2, 1, 0.5, 0.25 mg/L; internal controls 3 and 0.4 mg/L) in a diluent containing an equivalent amount of protein to that of the test sample i.e. pooled human serum (Bradshaw Biologicals) diluted in pH 6.6 phosphate buffer to give varying concentrations of protein.

The test samples were assayed undiluted and diluted in a buffer with an equivalent amount of protein (for most samples 1:10 and 1:20 dilutions were sufficient). Calibrators, internal controls and tests were applied in triplicate following a random pattern. 6 mm blotting paper discs (Whatman) were dipped into the sample, and incubated overnight at 30°C. Zones of inhibition were measured with an image analyzer (Kontron Vidas). Drug concentrations were measured with a calibration curve constructed with Bennett’s calculation. The lower limit of detection of the method was less than 0.12 mg/L. The within-assay coefficient of variation was 9.4%.

The drug assay was performed at Dudley Road Hospital, Birmingham UK.

**Results**

Ceftriaxone was tolerated well by both the intravenous and intramuscular route with no reported adverse effects. The predictable pain of the intramuscular injection was minimised by reconstituting the crystalline powder in 3.5 mL of 1% lignocaine according to the manufacturer’s instructions. Ceftriaxone pharmacokinetics in serum and pleural fluid after a single intravenous and intramuscular injection are shown in Figures 1 and 2.

After a single injection, mean peak serum concentrations of 199 mg/L (S.E.M. 63.2) and 80.5 mg/L (S.E.M. 12.0) were obtained respectively after intravenous and intramuscular administration at 1 h. Mean trough serum concentrations were 27.5 mg/L (S.E.M. 12.6) after intravenous administration and 29.7 mg/L (S.E.M. 5.2) after intramuscular administration at 24 h. The area under the plasma concentration time curve (AUC) between 1 and 24 h were 1570 mg/L/h (S.E.M. 450) for intravenous administration and 1225 mg/L/h (S.E.M. 123) for intramuscular administration. The serum half-life of the drug was 8.1 h (S.E.M. 1.6) and 17.7 h (S.E.M. 3.5) in the intravenous and intramuscular groups respectively. The mean volume of distribution calculated by extrapolation was 7.8 L (S.E.M. 2.2) for the intravenous group, and 11.8 L (S.E.M. 0.8) for the intramuscular group (Table II). Plasma clearance was 0.83 L/h (S.E.M. 0.34) for the intravenous group and 0.57 L/h (S.E.M. 0.22) for the intramuscular group.
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In pleural fluid a mean peak concentration of 20.1 mg/L (S.E.M. 4.7) was achieved 6 h after intravenous injection and a mean peak concentration of 15.3 mg/L (S.E.M. 5.1) was achieved 12 h after intramuscular injection on the first day of administration. The corresponding mean trough concentrations were 9.6 mg/L (S.E.M. 1.9) following intravenous injection and 13.3 mg/L (S.E.M. 3.1) following intramuscular injection at 24 h. The mean AUC between 1 and 24 h for pleural fluid was 282 mg/L/h (S.E.M. 240) for the intravenous group and 353 mg/L/h (S.E.M. 77) for the intramuscular group (Table II).

We calculated fluid/serum concentration ratios of ceftriaxone 12 h after injection, by which time both intravenous and intramuscular curves had plateaued. The concentration ratio was 0.27 (S.E.M. 0.11) in the intravenous group, ranging widely from 0.01 to 0.63, and 0.29 (S.E.M. 0.10) in the intramuscular group (range 0.04–0.60).

Figure 1. Blood (△) and pleural fluid (▲) kinetics of ceftriaxone on the first day of administration after intravenous injection. Results are means (±S.E.) of six determinations.

Figure 2. Blood (△) and pleural fluid (▲) kinetics of ceftriaxone on the first day of administration after intramuscular injection. Results are means (±S.E.) of seven determinations.
Statistical comparisons of peak concentration, trough concentration, AUC and half-life, volume of distribution and plasma clearance were carried out between the intravenous and intramuscular groups using the Mann-Whitney test (Table II). None of the differences was significant.

The serum and pleural fluid kinetics on the fourth day of intramuscular administration are illustrated in Figure 3. The mean peak serum concentration on the fourth day of administration was 125.9 mg/L (S.E.M. 12.1) and the mean serum trough concentration was 56.7 mg/L (S.E.M. 12.5). The mean peak pleural fluid concentration was 54.4 mg/L (S.E.M. 14.9) and the mean trough level was 35.0 mg/L (S.E.M. 10.8). These figures, which appear higher than those obtained for the first day of administration, are
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consistent with accumulation of the drug with repeated administration, though with this number of patients the difference did not reach statistical significance. The mean pleural fluid/serum concentration ratio at 12 h on day 4 was 0.54 (S.E.M. 0.14).

Discussion

Following a single intravenous injection, a mean serum peak concentration of 199 mg/L (S.E.M. 63.2) at 1 h and a mean serum trough concentration of 27.5 mg/L (S.E.M. 12.6) at 24 h were obtained. These values were higher than those obtained by Benoni et al. (1986) and Scaglione, et al. (1990). However, following intramuscular administration, the mean serum peak concentration was lower at 80.5 mg/L (S.E.M. 12.0) at 1 h though with a comparable trough concentration of 29.7 mg/L (S.E.M. 5.2) at 24 h.

The MICₘ of ceftriaxone for the two most common respiratory pathogens are as follows, *H. influenzae* 0.008 mg/L, *S. pneumoniae* 0.025 mg/L. The serum trough concentrations achieved after a single injection of ceftriaxone by either the intravenous or intramuscular route is clearly well above the MIC for those two organisms, and is also well in excess of the MICₘ for the less common respiratory pathogens such as *Staphylococcus aureus* 3.7 mg/L, *Klebsiella* species 0.6 mg/L, (Emmerson et al., 1985) and *Moraxella catarrhalis* 1.0 mg/L (Knapp, Sierra-Madero & Washington, 1988). This implies that a single injection of ceftriaxone given intramuscularly provides adequate blood concentrations against common respiratory pathogens for beyond 24 h.

In the group of patients receiving intramuscular ceftriaxone the serum mean peak and mean trough concentrations were higher at 125.9 mg/L (S.E.M. 12.1) and 56.7 mg/L (S.E.M. 12.5) respectively on the fourth day of administration when compared to the first day. This is consistent with a potentially desirable cumulative effect.

Following intravenous administration ceftriaxone penetrates into the pleural cavity achieving a mean peak concentration of 20.1 mg/L (S.E.M. 4.7) at 6 h when compared with peak serum concentrations which are achieved at 1 h, a time lag of 5 h is demonstrated between peak serum and pleural fluid concentrations. The pleural fluid ceftriaxone concentrations did not exceed serum concentrations at any time during the twenty four hour period. This suggests that in our group of patients with pleural effusions of non-infective origin the antibiotic did not show preferential uptake into the pleural cavity.

After intramuscular injection a mean peak pleural fluid concentration of 15.3 mg/L (S.E.M. 5.1) was achieved 12 h after injection and the mean trough concentration of 13.3 mg/L (S.E.M. 3.1) at 24 h being somewhat higher than that achieved following intravenous administration. On the fourth day of intramuscular administration the mean peak pleural fluid concentrations had increased to 54.4 mg/L (S.E.M. 14.9) and the mean trough concentrations had increased to 35 mg/L (S.E.M. 10.8). At these concentrations, ceftriaxone should provide cover against most common respiratory pathogens.

Pleural fluid may be considered a model of extracellular fluid (Landis & Pappenheimer 1963). This study demonstrates that ceftriaxone penetrates into the extravascular compartment of the body and achieves antibiotic concentrations in the extracellular fluid well in excess of the MICs for common typical respiratory pathogens and hence would be a suitable antibiotic to treat typical lower respiratory tract infections. Furthermore, these antibiotic concentrations could be achieved and maintained using a single intramuscular injection of the antibiotic. This has a significant
cost saving potential in a budget-conscious health service in that the antibiotic could be given on domiciliary basis in patients requiring parenteral therapy.

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References


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