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Determination of vancomycin trough level in serum and cerebrospinal fluid of patients with acute community-acquired meningitis: A prospective study

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Summary *Background:* Penetration and concentration of vancomycin is still an elusive and complex issue particularly in Cerebrospinal Fluid (CSF). The aim of this study was to clarify the penetration of this antimicrobial agent in CSF during meningeal inflammation.
Methods: In a prospective study, adult patients, with clinical and CSF analysis compatible with acute meningitis, who received vancomycin (15 mg/kg loading and 30 mg/kg daily maintenance dose) with ceftriaxone (4 gr/daily) were enrolled. CSF analysis including vancomycin trough levels before the fourth maintenance dose and during the 8–10th days of treatment, and simultaneous serum levels were performed by High-Pressure Liquid Chromatography (HPLC).
Results: Twenty-seven patients (18 men, 9 women; mean age of 39.4 ± 14.7) were enrolled. The first serum trough level of vancomycin was 13.82 ± 1.28 mg/l. The mean of corresponding trough level in CSF was 11.2 ± 1.41 mg/l. The serum and CSF trough levels revealed positive linear correlation (*r*: 0.60) and was significant at the 0.01 level (P: 0.004). The penetration CSF/serum ratio was 0.811 ± 0.082 (coefficient of variation: 10.1%). The second trough levels of serum and CSF in (14 patients) vancomycin were 13.32 ± 1.02 and 10.64 ± 1.21, respectively. The serum and CSF trough levels revealed positive linear correlation (*r*: 0.71). The serum and CSF concentrations revealed no variation compared to the first trough levels.

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Conclusion: Vancomycin has appropriate concentration in CSF during the treatment of meningitis and do not decrease along with the alleviation of meningeal inflammation in spite of concerns in this regard.

Introduction

Acute meningitis, particularly with a bacterial cause, is a well-known life threatening condition. It is a true medical emergency and requires prompt diagnosis and treatment. Recently, the emergence of resistant pathogens has influenced the medical strategies and selection of antimicrobial agents. Vancomycin and cephalosporins are currently the antibiotics of choice for empirical therapy of acute meningitis.

Vancomycin is a large glycopeptide with a high molecular weight.[1] Its oral absorption is not significant, and the main route of elimination is renal excretion.[2] The pharmacokinetic profile of vancomycin is complex and there are still many unresolved issues. In patients with normal glomerular filtration rate, vancomycin seems to have a maximum distribution phase of 1 h, a volume of distribution of 0.4—1 l/kg, and an elimination half-life of 6—12 h[3] The range of protein binding is estimated to be 10—50%.[3] Constitutionally, vancomycin is a time-dependent antibiotic, and the activity is influenced by several factors including the distribution, the inoculum size, and the protein-binding effects. Vancomycin penetrates into most of the body spaces with variable concentrations, depending, to some extent, on the degree of inflammation.[3]

Since the Cerebrospinal Fluid (CSF) penetration of hydrophilic antibiotics including penicillins, cephalosporins, or vancomycin is strongly influenced by meningeal infiammation, there are some concerns over the administration of high-dose steroids.[4,5] Vancomycin was reported to penetrate into the inflamed meninges, with CSF concentrations of 6.4—11.1 mg/l and CSF-to-serum ratios of 0.36—0.48.[3] In addition to the anti-inflammatory agents (steroids), abating of the meningeal inflammation during the treatment may also influence the CSF penetration of antibiotics. In patients with intact meninges, vancomycin penetration into the CSF was reported to be fairly low, as it was shown by a CSF concentrations of 0—3.45 mg/l, with corresponding CSF-to-serum ratios of 0—0.18.[3]

There have been very few human studies on the pharmacodynamics of vancomycin, most of them with inconclusive findings in determining parameters reliably predicting patients' outcomes. The majority of these studies have involved relatively small populations of patients with a variety of infection types. The therapeutic range often quoted for vancomycin monitoring is peak and trough serum concentrations of 30—40 and 5—10 mg/l, respectively.[3] However, it should be noted that the practice of routine monitoring and adjusting of serum vancomycin concentrations has been the subject of intense debate for many years.[6] The controversy has resulted from conflicting evidence on the use of serum vancomycin concentrations for predicting drug-induced toxicity and also as a measure of effectiveness in treating infections.[6] Since vancomycin is a time-dependent antibiotic and there are practical issues associated with determining a precise peak serum concentration, most clinicians have abandoned the routine practice of determining peak serum concentrations and relied solely on monitoring trough serum concentrations for this antibiotic.[3]

Owing to the lack of data and presence of substantial differences among the previous studies regarding the setting, patients, and applied methods for therapeutic drug monitoring, this study was conducted to determine CSF vancomycin concentrations in patients with acute meningitis and its connection with serum levels of the drug during the therapy.

Materials and methods

This prospective study was carried out in Loghman Hospital, Tehran, Iran in 2012 and 2013. All patients aged 18—60 years who were admitted to our center with clinical presentations suggestive of acute meningitis including fever (>38 °C), headache, nausea and/or vomiting, meningeal irritation signs, and nuchal rigidity with or without alternation in consciousness were recruited to the study. For all of the patients, the time between initiation and stabilization of the signs and symptoms was less than 24 h. The clinical presentation of the patients was associated with pleocytosis (polymorphonuclear (PMN) cell count >1 mm^3), with or without hypoglycorrhachia (CSF glucose <40 mg/dl or less than half of the simultaneous blood glucose levels) and elevated CSF protein (>50 mg/dl) or bacteria in direct gram smear. All of the patients had normal creatinine clearance (>90 ml/min) based on estimation equation (Cockroft—Gault formula).[7] They received empirically vancomycin (15 mg/kg loading dose followed by 30 mg/kg daily maintenance divided into two doses, infused intravenously within 1 h) and ceftriaxone (2 g, twice daily, intravenously) without dexamethasone. Patients with other treatment regimens or those who underwent escalation or de-escalation of antimicrobial agents were excluded from the study.

Other exclusion or withdrawal criteria were as follow: primary or secondary immune deficiency including HIV infection of any CD4 count, patients with solid or hematopoietic transplants, patients receiving steroids or other anti-inflammatory drugs, exclusion of acute meningitis during the therapy, initiation of antibiotics before admission for recent manifestations, hospitalization during the last three months before admission, and disinclination of the patients to stay in the study.

To determine vancomycin trough level during the therapy, CSF and serum samples were obtained from the study patients 15—30 min prior to vancomycin infusion on the day 4 and between the days 8—10 of the treatment.

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