International Journal of Antimicrobial Agents 49 (2017) 603–608

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Pharmacokinetics and cerebrospinal fluid penetration of norvancomycin in Chinese adult patients

Jun Li, Shengquan He, Zhiping Yang, Congxia Lu *

The First Affiliated Hospital of Xiamen University, No. 55 Zhenhai Road, Siming District, Xiamen, Fujian 361003, China

ARTICLE INFO

Article history:
Received 19 October 2016
Accepted 6 January 2017

Keywords:
Norvancomycin
Meningitis
CSF penetration
HPLC
Human
Pharmacokinetics

ABSTRACT

Norvancomycin is an antibiotic that has been approved for the treatment of infections caused by antibiotic-resistant Gram-positive bacteria and has been used in China for more than a decade. However, the cerebrospinal fluid (CSF) penetration of norvancomycin has not been evaluated. The aims of the study were (i) to investigate the pharmacokinetics and CSF penetration of norvancomycin in meningitis and non-meningitis patients and (ii) to recommend favourable dosing regimens in meningitis patients. Twenty adult patients (ten with meningitis and ten without meningitis) requiring norvancomycin treatment were enrolled. All patients received a norvancomycin regimen of 800 mg every 12 h. Blood and CSF samples were consecutively collected up to 12 h after the end of the fourth 60-min infusion. Norvancomycin concentrations both in serum and CSF were measured using a high-performance liquid chromatography (HPLC) assay. CSF penetration of norvancomycin was evaluated by calculating the CSF/serum ratio. Mean norvancomycin serum trough levels were 9.9 ± 1.44 μg/mL in patients with meningitis and 10.08 ± 1.12 μg/mL in patients without meningitis ($P > 0.05$). In addition, norvancomycin penetrated into the inflamed meninges, with mean CSF concentrations of 3.93–10.52 μg/mL and mean CSF/serum ratios of 0.18–0.43, both of which were significantly higher than in patients without meningitis ($P < 0.05$). These results suggest that norvancomycin has higher CSF penetration in patients with meningitis compared with other groups and that norvancomycin is effective in treating patients with purulent meningitis at a comparably low dose.

1. Introduction

Bacterial meningitis is a well-known life-threatening disease and continues to inflict a heavy burden on patients in less developed countries [1], especially with the continuing increase in the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) [2]. Treatment of MRSA-induced infections mainly depends on glycopeptide antibiotics. Vancomycin, a representative of the glycopeptide class, has been the cornerstone of treatment of patients with serious MRSA infections [3]. However, reduced vancomycin susceptibility is prevalent worldwide, with rising minimum inhibitory concentrations (MICs) of vancomycin among vancomycin-susceptible *S. aureus* (vancomycin 'MIC creep') [4]. The efficacy of an antimicrobial agent for therapy of bacterial meningitis depends on whether the causative organism is susceptible, the activity of the antimicrobial in purulent cerebrospinal fluid (CSF) and especially its ability to penetrate the blood–brain barrier (BBB).

Norvancomycin, another glycopeptide antimicrobial agent, was independently developed by Chinese scientists. It differs from vancomycin only in that $-NHCH_3$ at the peptide amino terminal of vancomycin has been replaced by $-NH_2$, with a comparable antibacterial spectrum and antibacterial activities to those of vancomycin. Moreover, norvancomycin is much cheaper than vancomycin and has been used widely in China for more than a decade. However, similar to vancomycin, potential toxicities [5,6], such as nephrotoxicity, ototoxicity, rash and itching, are a major concern in using this antibiotic. Therefore, monitoring serum concentrations is important to predict drug-induced side effects and to measure drug efficacy when treating infections.

Despite abundant information about the monitoring of serum vancomycin levels, data on norvancomycin are limited. Only experimental animal models have provided information about drug distribution in tissues [7]. These studies have shown that norvancomycin cannot permeate through the BBB [7]; however, little is known about the CSF penetration of norvancomycin in humans. In addition, very few human studies have investigated norvancomycin concentrations in the CSF [8]. In the present study,

* Corresponding author. The First Affiliated Hospital of Xiamen University, No. 55 Zhenhai Road, Siming District, Xiamen, Fujian 361003, China. Fax: +86 592 213 7509.
E-mail address: 13959219339@126.com; zhiping111@126.com (C. Lu).

http://dx.doi.org/10.1016/j.ijantimicag.2017.01.014
0924-8579/

we investigated the pharmacokinetics and CSF penetration of norvancomycin by concurrently monitoring CSF and blood norvancomycin levels in ten meningitis and ten non-meningitis patients receiving norvancomycin therapy.

The aims of the study were (i) to investigate the pharmacokinetics and CSF penetration of norvancomycin following intravenous (i.v.) administration in meningitis and non-meningitis patients and (ii) to recommend favourable dosing regimens for meningitis patients.

2. Materials and methods

2.1. Patients and study design

This prospective study was performed in the First Affiliated Hospital of Xiamen University (Xiamen, Fujian, China) from November 2013 to March 2015. All patients of either sex aged 18–60 years who were admitted to the hospital and who were infected with norvancomycin-sensitive bacteria without alterations in consciousness were enrolled in the study. Of these patients, ten had meningitis with clinical and CSF analyses compatible with acute meningitis and ten were non-meningitis patients with Gram-positive bacterial infections requiring norvancomycin treatment. All of the patients had normal CSF routine biochemical examinations and estimated creatinine clearance (CL_{Cr}) (>90 mL/min) based on the Cockcroft–Gault formula [9]. The patients empirically received i.v. norvancomycin hydrochloride (trade name Wanxun; North China Pharmaceutical Group Corporation, Shijiazhuang, Hebei, China; batch no. 13040011) at a dose of 800 mg every 12 h (q12h) with a 60-min infusion time. All of the enrolled patients had an intra-arterial line in situ for frequent collection of blood samples and all patients underwent lumbar puncture, with a catheter left to collect CSF. The hospital's Ethical Committee approved the study, and all patients voluntarily joined the study and provided their informed consent.

Exclusion criteria included renal dysfunction, chronic infection lasting >4 weeks and an expected hospital stay of <72 h. Other withdrawal or exclusion criteria were as follows: patients with abnormal liver function; primary or secondary immune deficiency, including human immunodeficiency virus (HIV) infection; CSF circulation disturbances such as scoliosis; solid or haematopoietic transplants; and patients receiving steroids or other anti-inflammatory drugs.

2.2. Collection and processing of cerebrospinal fluid and blood samples

To achieve steady-state conditions, samples were collected on Day 2. Serial blood samples were collected from an arterial line catheter at 0, 0.5, 1, 2, 4, 6, 8 and 12 h after the end of the fourth administration of i.v. norvancomycin. Simultaneously, CSF samples were obtained by lumbar puncture from the catheter. All samples were centrifuged and the supernatants were collected and stored at –80 °C until assay.

2.3. Determination of norvancomycin concentrations by high-performance liquid chromatography (HPLC)

Norvancomycin concentrations were determined using a Waters ACQUITY UPLC BEH C18 column (2.1 mm × 50 mm; 1.7 μm; Waters Corp., Milford, MA) equipped with an ultraviolet detector system. The mobile phase consisted of methyl alcohol (0.5 mol/L)/dipotassium phosphate (0.05 mmol/L, pH 3.2) in a 12:88 (v/v) ratio at a flow rate of 0.21 mL/min at 42 °C. Detection was performed at a wavelength of 236 nm. The sample pre-treatment process was based on protein precipitation followed by ultrafiltration. All tested solutions were filtered through 0.22 μm filters prior to use. Vancomycin was used for internal standardisation. The norvancomycin concentration–time curve was measured and the relationship between norvancomycin CSF and plasma levels was calculated.

2.4. Pharmacokinetic (PK) analysis

PK analysis was performed by the non-compartmental method using WinNonlin Professional v.5.2.1 (Pharsight Corp., Mountain View, CA). The following PK parameters were determined: terminal elimination half-life ($t_{1/2}$); area under the concentration–time curve (AUC); and clearance (CL).

2.5. Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics v.19.0 (IBM Corp., Armonk, NY). Results are expressed as the mean ± standard deviation (SD). Significant differences between two groups were determined by Student's *t*-test or analysis of variance (ANOVA) for repeated measurement data with a 0.05 significance level.

3. Results

3.1. General clinical conditions of the patients

A total of 20 patients (10 with meningitis and 10 without meningitis) were included in the study (11 male and 9 female). The mean age was 45.5 ± 10.1 years (range 28–60 years) for patients with meningitis and 49.8 ± 9.8 years (range 33–62 years) for non-meningitis patients. The CL_{Cr} for all enrolled patients was >90 mL/min. No significant differences were found in sex, age, body weight and CL_{Cr} between the patients with and without meningitis (Table 1). During the treatment phase, no adverse effects were observed, especially regarding renal function. The CL_{Cr} was >90 mL/min throughout the treatment period for all patients. At the end of the treatment course, most of the patients appeared to be in a normal status. In addition, clinical and bacteriological success was achieved, with the exception of one patient who experienced sudden death from other complications.

3.2. Norvancomycin concentrations in serum and cerebrospinal fluid

Mean serum and CSF norvancomycin concentrations are presented in Figs 1 and 2 for patients evaluated in the fourth 12 h of treatment (i.e. after the end of the fourth infusion). Norvancomycin concentrations were time-dependent both in serum and CSF, with peak concentrations achieved after 30 min of infusion. Mean serum norvancomycin levels in patients with meningitis were not significantly different from the levels achieved in non-meningitis patients (Fig. 1).

However, mean CSF norvancomycin concentrations in patients with meningitis were significantly higher than those achieved in non-meningitis patients at all examined time points (Fig. 2).

Peak and trough norvancomycin levels are shown in Table 2. The highest serum norvancomycin levels ranged from 39.81 μg/mL in Patient 20 to 74.78 μg/mL in Patient 16, whereas the trough levels ranged from 7.38 μg/mL in Patient 10 to 12.35 μg/mL in Patient 5. No significant differences were detected between patients with and without meningitis ($P > 0.05$). Patients with meningitis had maximum CSF levels ranging from 8.59 to 14.93 μg/mL (mean ± SD, 10.52 ± 1.98 μg/mL) and trough levels ranging from 3.24 to 4.62 μg/mL (mean ± SD, 3.93 ± 0.57 μg/mL), whereas non-meningitis patients had peak CSF levels ranging from 0.20 to 5.14 μg/mL (mean ± SD, 2.04 ± 1.99 μg/mL) and trough levels ranging from 0.04 to 1.84 μg/