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Exploration of Vancomycin Concentrations in Cerebrospinal Fluid and Plasma after Craniocerebral Surgery

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Abstract: Patients who underwent cranial hematoma removal, extra-ventricular drainage, intracranial arteriovenous malformation resection, and other craniotomy procedures and were administered vancomycin were selected. Cerebrospinal fluid (CSF) and plasma specimens were collected simultaneously from patients at different time points using the random number method, and vancomycin concentrations in CSF and plasma were determined by enzyme amplification immunoassay. The ratio of vancomycin in CSF to plasma concentration was calculated, and the medical records were analyzed to initially investigate the relevant factors that can affect the drug concentration or blood-brain barrier. The mean plasma concentration of vancomycin was 11.87±8.5μg/mL, the CSF concentration was 2.42±1.34μg/mL, and the cerebral blood ratio was 0.28±0.21. This study suggests that the transmission rate of vancomycin did not increase significantly after craniocerebral surgery; due to individual differences, CSF and plasma concentrations vary greatly, and drug concentration monitoring is recommended.

Keywords: Blood-Brain Barrier; Enzyme Amplification Immunoassay; Blood Drug Concentration; CSF Concentration

Introduction

Intracranial infection is one of the serious comorbidities after neurosurgery, and it is also a common and more serious nosocomial infection. The most common causative organisms are gram-positive *cocci*, which account for 39.8% to 55% of cases reported in China [1]. Studies have shown that intracranial infections caused by methicillin-resistant *Staphylococcus aureus* and coagulase-negative *staphylococci* have been on the rise year by year. Vancomycin is currently the first-line conventional drug for the treatment of such bacterial infections, but the existence of the blood-brain barrier and the increase in bacterial resistance make it difficult to achieve therapeutic effects.

Vancomycin is difficult to reach the cerebrospinal fluid (CSF) through the blood-brain barrier because of its large molecular weight, strong hydrophilicity, complex structure and the lack of an active transport system for vancomycin in the brain [2]. According to the literature, neurosurgical patients have a blood-brain barrier opening factor by surgical means, and theoretically CSF penetration rate should be higher [3]. In order to verify whether the transmission rate of vancomycin through the blood-brain barrier increases when the blood-brain barrier is disrupted, CSF and plasma specimens were randomly collected from patients with craniosynostosis, and the concentration of vancomycin in CSF and plasma was determined by enzyme amplification immunoassay, and the cerebro-blood ratio was calculated to evaluate the effect of surgery on the blood-brain barrier.

1. Methods

1.1 General information of the patient

Patients requiring vancomycin after craniosurgery, requiring ventricular drainage or lumbar puncture, with normal renal function before administration, no previous chronic organ insufficiency, and no history of vancomycin allergy were selected from 2017 to 2019 in the neurosurgery, emergency surgery, and intensive care units of a hospital.

1.2 Specimen collection and concentration determination

Plasma and CSF specimens were collected at the same moment using the random number method for different patients at different time points, and 1 to 2 mL of CSF and blood were collected at 0, 0.5, 2, 4, 6, 8, 10, 12, and 14 hours after input, respectively. The concentration was determined using the Syva® drug concentration analyzer Viva-E2000. Depending on the laboratory equipment and specimen collection, the measurement was generally done within 1 month.

1.3 Statistical Methods

The obtained drug concentrations were expressed as Mean±SD; SPSS21.0 software was used for analysis, and *t*-test was used for measurement, with $P<0.05$ indicating statistically significant differences.

2. Results

A total of 17 patients, 7 males and 10 females, aged 54±12 years and weighing 65±8 Kg, were included in this study. 9 patients suffered from subarachnoid hemorrhage, 2 ventricular hemorrhage, 4 cerebral hemorrhage, 2 severe closed cranial injury; 8 cases had hypertension and 2 cases had diabetes mellitus; 13 cases underwent hematoma removal and 4 cases had bilateral lateral ventricular drainage; intracranial infection was diagnosed in 9 cases and undiagnosed in 8 cases. 9 cases were diagnosed with intracranial infection and 8 cases were not diagnosed with intracranial infection; CSF samples were collected by lumbar puncture in 13 cases and ventricular drainage in 4 cases.

2.1 Concentration in plasma

The highest concentration of vancomycin in plasma was 40.7 μg/mL, the lowest concentration was 3.7 μg/mL, and the mean value was 14.53 ± 10.53 μg/mL. The blood concentration showed a gradual decrease with time.

2.2 Concentration in CSF

The highest concentration of vancomycin in CSF was 11.6 μg/mL, the lowest concentration was 1.1 μg/L, and the mean value was 3.33 ± 2.76 μg/mL. The CSF concentration showed a trend of increasing and then decreasing over time.

2.3 Cerebral blood ratio

The maximum value of cerebral blood ratio was 0.62, the minimum value was 0.03, and the mean value was 0.28±0.21. Correlation analysis of cerebral blood ratio with time using SPSS showed that Pearson correlation coefficient: 0.584, $P=0.028$.

The bright blood ratio was positively correlated with time and had a strong correlation. The regression curve equation was Y=0.07+0.03*X.

3. Discussion

Among the 17 patients in this study, 7 patients improved with conventional doses of vancomycin, while only 4 patients were in a critical state, 5 in a light coma and 1 in a deep coma.

3.1 Vancomycin blood concentration after cranial surgery

The total 17 sets of data measured vancomycin T_{max} is 0.58h, C_{max} is 34μg/mL, $t_{1/2}$ is 5.33h. C_{min} is 3.7μg/mL, according to the Expert Consensus on Clinical Application of Vancomycin[4], the mean peak concentration of vancomycin is 63μg/mL at the end of titration after multiple doses of 1g 1h, vancomycin blood concentration should be clinically controlled at 10-20μg/mL, at least 10μg/mL. The peak concentration in this experiment was lower than 63 μg/mL, and the lowest concentration was not completely controlled above 10 μg/mL, which indicates that the conventional dose of drug administration may not achieve effective therapeutic effect, and the dose may have to be increased during clinical treatment, and it is recommended to monitor the drug concentration, of course, due to the limitation of sample size. This requires further expansion of the sample size for validation. The half-life of normal renal function is 4-6 h. The $t_{1/2}$ of this experiment is within the normal range. This may be related to the half-life calculated in this experiment, because the experiment was only taken once for different patients at different time points, so the half-life obtained with the time when the blood concentration dropped to half, the error is relatively large; of course, it may also be related to the sampling time error, specimen transfer storage, and other factors.

3.2 Vancomycin concentration in CSF after cranial surgery

In total, 17 sets of data were measured in which the CSF concentration C_{max}: 4.3μg/mL (8h); C_{min}: 1.1μg/mL (0h), 1.3μg/m (14h), indicating that vancomycin reached steady state in the CSF; according to previous literature [4], the concentration of CSF is 0-4μg/mL when there is no inflammation in the meninges, and the concentration can reach 6.4-11.1μg/mL when there is inflammation. 6.4 to 11.1 μg/mL, and the CSF concentrations measured in this experiment were basically in the range of 0 to 4 μg/mL, so craniotomy broke the blood-brain barrier, and the concentration of vancomycin in the CSF did not increase significantly; the standard deviation of CSF concentrations was large, indicating that the concentration of CSF caused by individual differences also varied greatly, so drug concentration monitoring should be performed; after craniotomy, intravenous drip failed to significantly increase the vancomycin concentration, so in the process of clinical treatment, for patients with serious cranial infection, intrathecal injection intrathecal injection can be used when necessary to repeatedly administer the drug in a short period of time, so that the drug can rapidly reach therapeutic concentration in the CSF [5].

3.3 Cerebral blood ratio analysis

The standardized CSF transmission rate should be calculated as the ratio of the area under the concentration-time curve of CSF to plasma drug, but because the sample size of this experiment was small and only one CSF and plasma sample was collected in each patient, the ratio of CSF concentration to plasma concentration was used to approximate the CSF transmission rate called cerebrohematocrit. The maximum value of cerebral blood ratio is 0.62, the minimum value is 0.03, and the mean value is 0.28±0.21, which indicates a great variation among individuals. According to the study, when the blood-brain barrier is disrupted, the CSF penetration rate is 22% [6], and the cerebral blood ratio in this experiment is higher than the penetration rate of this study. According to the report [6], the penetration rate of vancomycin through the CSF

increases after the blood-brain barrier is disrupted, but this is only a single factor, and when inflammation occurs after craniocerebral surgery due to the accumulation of bacterial acidic metabolites, it leads to a decrease in the pH of the CSF, causing an increase in the pH gradient of the blood CSF, while favoring the movement of antibacterial drugs into the CSF. Therefore, when craniotomy is complicated by meningitis, the transmission rate of CSF increases.

Conclusion

The results of this study indicate that the blood-brain barrier was disrupted after craniotomy, and the transmission rate of vancomycin in CSF did not increase significantly, not as much as when there was inflammation in the meninges; according to the data of this study, the plasma concentration and CSF concentration of different patients after craniotomy varied greatly, and drug concentration monitoring is recommended.

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