Association Between Vancomycin Blood Brain Barrier Penetration and Clinical Response in Postsurgical Meningitis

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ABSTRACT - PURPOSE: This study investigated the association between vancomycin blood brain barrier penetration and clinical response in patients with postsurgical meningitis. **METHODS:** Adult patients with postsurgical meningitis were recruited. Eligible patients received vancomycin 500 mg every 6 h for at least 5 days. On day 3 or 4, cerebrospinal fluid (CSF) and simultaneous serum samples were obtained to determine CSF minimum concentrations (C_{min}), serum C_{min} and CSF to serum C_{min} ratio. **RESULTS:** Twenty-two patients (14 men and 8 women; mean age of 52.6± 12.1 years) were recruited. The vancomycin C_{min} was 3.63 ± 1.64 mg/L in CSF and 13.38 ± 5.36 mg/L in serum, with the CSF to serum C_{min} ratio of 0.291 ± 0.118. The C_{min} in serum and in CSF showed a significant correlation (p=0.005, r =0.575). The vancomycin CSF C_{min} had a significant correlation with the decline of white blood cell counts (WBCs) in CSF (p=0.003, r =0.609). CSF $C_{min,}$ serum C_{min} and CSF to serum C_{min} ratio all showed no significant correlation with clinical response (p=0.335, 0.100, 0.679, respectively). **CONCLUSIONS:** There was a positive correlation between serum C_{min} and CSF C_{min}. However, only CSF C_{min} is positively correlated with WBCs improvement in CSF. All other parameters such as serum C_{min}, CSF C_{min} and CSF to serum C_{min} ratio had no correlation with clinical response.

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INTRODUCTION

Central nervous system (CNS) infection such as meningitis, is one of the serious complications in neurosurgical procedures. A recent meta-analysis in post-neurosurgical patients showed that the overall CNS infection was 4.24%, and Gram-positive bacteria was the most common pathogen, accounting for approximately 61.7% of the isolates (1). As resistance to cephalosporins and other β-lactams is increasing, vancomycin has become the antibiotic of choice to eradicate *methicillin-resistant Staphylococcus aureus* (MRSA). Vacomycin has poor penetration into the cerebral spinal fluid (CSF) (2). The penetrability of vancomycin depends on the degree of meningeal inflammatory when given intravenously (3). Insufficient vancomycin dosage is one of the major proposed causes of treatment failure in MRSA infections (3). Published pharmacokinetics studies on vancomycin in patients with meningitis are mainly focused on vancomycin concentrations in the CSF and/or serum, but not on the CSF exposure-effect relationship (4-7). Using concentrations of vancomycin in serum to predict the clinical response in patients with meningitis remains controversial. The primary objectives of this study were i) to determine the correlation between vancomycin concentrations in CSF and in serum,a nd ii) to determine the association between vancomycin blood brain barrier (BBB) penetration and clinical response in patients with postsurgical meningitis.

METHODS

Patient population

This prospective study was conducted in the Second Xiangya Hospital of Central South University between May 2014 and June 2015.

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The study was carried out according to the declaration of Helsinki and was approved by the Second Xiangya Hospital of Central South University Ethics Committee. All patients consented to participate in the study. All patients aged 18 or older, who were hospitalized in Neurosurgery ward with proven or highly suspected postsurgical meningitis were recruited to the study. Postsurgical meningitis was defined as two or more of the following criteria:1) clinical signs and symptoms such as fever (temperature greater than or equal to 38°C), headache, vomiting, any meningeal signs, such as, neck rigidity or loss of consciousness;2) at least two of the changes in CSF specimens: white blood cells(WBCs) count more than 1000×10^6/L with coenocyte predominance (>50%), glucose concentrations <2.5 mmol/L, protein concentrations >500 mg/L; 3) either positive result in gram stain culture from the CSF or positive CSF culture (8,9). All patients received either vancomycin alone or combination therapy with ceftriaxone. All patients had normal hepatic function (serum alanine aminotransferase, (ALT) 9.0-50.0 μ/L; serum aspartate aminotransferase, (AST), 15.0-40.0 μ/L; total bilirubin, (TBIL), 5.1-17.1 μmol/L; direct bilirubin, (DBIL), 0-6.0 μmol/L; albumin, (ALB), 40.0-55.0 g/L)and renal function (blood urea nitrogen, BUN, 2.90-7.14 mmol/L; serum creatinine, S_{cr}, 40.0-133.0 μmol/L; fluid input and urinary output before vancomycin administration.

The exclusion criteria were as follows:

1) Patients treated with vancomycin 3 days before recruitment to the study;
2) Patients already receiving both intravenous and intraventricular infusion of vancomycin;
3) Patients with hypersensitivity to vancomycin;
4) Patients with hepatic or renal insufficiency as defined by normal limits.

Demographic and clinical data of the patients included gender, age, weight, height, co-morbidities, and concomitant drugs were collected. Daily laboratory parameters included WBCs, glucose concentrations and protein concentrations in CSF, S_{cr}, BUN, complete blood count were collected and recorded. Body temperature were monitored every 8 hours during the treatment course. Duration of vancomycin therapy, days to afebrile (temperature <38 C), normal indexes in CSF (WBCs<8×10^6/L, glucose concentrations, 2.50-4.50 mmol/L, protein concentrations, 150.00-450.00 mg/L) and CSF culture resolution were obtained. The estimated creatinine clearance was calculated based on *Cockcroft-Gault* formula.

Drug administration and sample determination

Vancomycin was administrated 500 mg intravenously (*iv*) every 6 hours (infused over 1 hour) for alone or in combination with Ceftriaxone (2 g *iv* twice daily). All patients did not administrate corticosteroids during the Vancomycin therapy. CSF and serum samples were collected for vancomycin concentrations by lumbar puncture or lumbar drainage on the day 3 or 4. CSF and serum samples were obtained simultaneously from study patients 5 hours after the end of infusion, to determine the vancomycin minimum concentration (C_{min}). Vancomycin concentrations were analyzed and CSF to serum C_{min} ratio was calculated as BBB penetration rate.

Clinical response

The clinical response was evaluated by patients' attending physicians and pharmacists together on the basis of patients' clinical signs and symptoms of meningitis (including fever, headache, neck rigidity, *Brzezinski's* and *Kerning's* signs), and laboratory indexes (including biochemical and microbiological examination of CSF), which were observed at baseline (admission) and during hospital stay. Patients' defined clinical response was agreed by the treatment team. Cure was defined as all resolution of clinical signs and symptoms of infections, all CSF indexes normalization (including glucose concentrations, protein concentrations and WBCs count), negative culture and gram stain of CSF, and no extra use of other antimicrobial agent. Improvement was defined as partial resolution of clinical signs and symptoms of infection; or CSF indexes obviously improving but not completely returning to normal. Failure was defined as more than 5 days with persistent clinical signs and symptoms of infections and obviously worsening CSF indexes; or persistent positive cultures or gram stain of CSF after 5 days of vancomycin therapy; or a change to another antimicrobial agents (linezolid in particular) against Gram-positive bacteria after 5 days of vancomycin therapy.

The adverse reactions

Daily monitoring of flushing, erythema, urticarial and pruritus for Red Man syndrome due to rapid infusion rate. Nephrotoxicity is a potential side effect from vancomycin. Vancomycin-induced nephrotoxicity was defined as a repeated (at least two consecutive) increased creatinine concentrations in serum of 44.2 μmol/L, or ≥50% increase from baseline without an obvious explanation (10, 11).

Also, blood and the lymphatic system disorders (including thrombocytopenia, neutropenia, agranulocytosis and eosinophilia) were monitored (12).

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) version 17.0 was used for descriptive statistical analysis. Mean values and standard deviation were determined for all continuous variables. Vancomycin serum C_{min} were stratified into two groups (<15 and ≥15 mg/L, a consensus review recommended vancomycin serum C_{min} at least 15 mg/L to achieve AUC /MIC≥400) (13). Independent sample 2 tail *t*-test and *Fisher's* exact test were used for comparison of data in the two groups. The rank correlation was used to analyze the association between vancomycin concentrations (including serum C_{min} and CSF C_{min}) and clinical response, and between BBB penetration rate and clinical response. Pearson's *r* coefficient was used to evaluate the correlation between vancomycin C_{min} and decline of WBCs in the CSF. $p \leq 0.05$ were considered statistically significant.

RESULTS

Twenty-two patients (14 men and 8 women) (**Table 1**) with proven or highly suspected postsurgical meningitis were included in the study. The mean age (±*SD*) was 52.6±12.1 years (range, 25-74 years). The baseline mean (±*SD*) glucose concentrations, protein concentrations and WBCs count in the CSF were 2.34 ± 1.26 mmol/L, 2671.59 ± 60.11 mg/L, 1819.1×10^6 /L, respectively. All patients had normal creatinine clearance. Six patients (patients 2, 3, 4, 7, 9 and 13) had positive CSF cultures, and the isolated organisms were *Streptococcus pneumoniae* (*S.pneumoniae*), *Enterococcus faecium* (*E.faecium*), *Staphylococcus aureus* (*S.aureus*), *Coagulase-negative staphylococcus*, *Staphylococcus saprophyticus* (*S.saprophyticus*) and *Enterococcus hirae* (*E.hirae*), respectively. After 3 days of therapy, all CSF cultures were negative.

The mean vancomycin C_{min} was 3.63 ± 1.64 mg/L in CSF and 13.38 ± 5.36 mg/L in serum, and the corresponding CSF to serum C_{min} ratio was 0.291 ± 0.118 (Table 1). The serum and CSF C_{min} displayed a weak positive correlation (p=0.005, r=0.575) (Figure 1). After 3-5 days of therapy, all patients showed amelioration of initial signs and symptoms, and were afebrile. Among them, 54.5% (12/22) were cured, and 45.5% (10/22) improved after 3-5 days. Vancomycin was continued beyond 5 days in two of the patients with improved signs and symptoms and lumbar drainage was obtained during the extended therapy. Meropenem 2 g *iv* every 8 hours was initiated in one of the two patients after 3 days of vancomycin therapy. The remaining 8 improved patients were treated with intravenous combined with intraventricular vancomycin 10 mg every other day for 10 days before cure was obtained. No vancomycin-induced nephrotoxicity was observed in all patients and serum creatinine concentrations remained stable during the study.

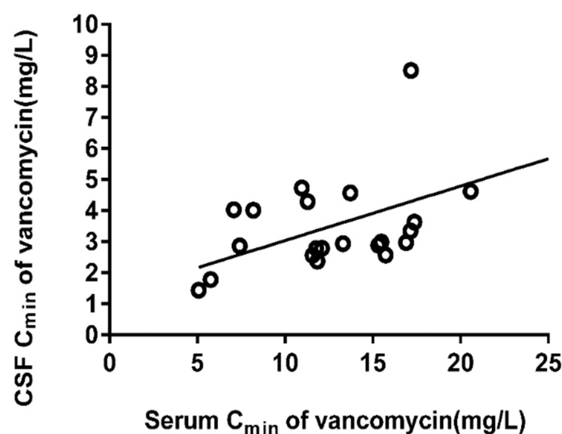

Figure 1. Correlation between vancomycin minimum concentrations in CSF and serum, 22 samples(r=0.575, p=0.005). The boldface dot shows two similar data.

Patients achieved cure and those with clinical improvement had no statistical significant difference in CSF C_{min}, serum C_{min} and CSF to serum C_{min} ratio (p=0.578, t=0.565; p=0.084, t=1.818; p=0.394, t=-0.871). There was no significant difference in clinical response between patients with serum C_{min} over 15 mg/L and under 15 mg/L (p=0.666). A positive correlation between the CSF C_{min} and the decline of WBCs in the CSF was obtained after vancomycin treatment (p=0.003, r =0.609) (**Figure 2**), while no significant correlation between the serum C_{min} or CSF to serum C_{min} ratio and the decline of WBCs in the CSF (p=0.295, r =0.240; p=0.294, r =0.240, respectively). CSF C_{min}, serum C_{min} and CSF to serum C_{min} ratio had no significant correlation with clinical response (p=0.335, r_s=-0.216; p=0.100, r_s=-0.360; p=0.679, r_s=0.094, respectively).

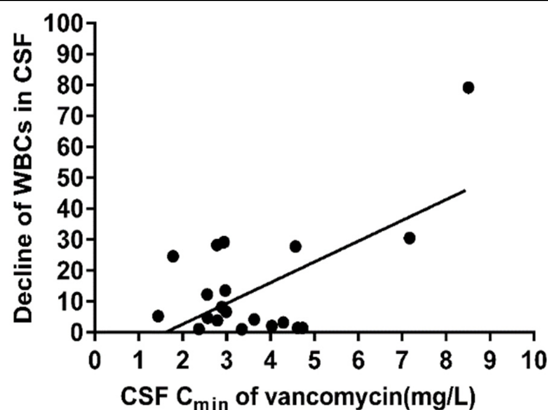

Figure 2. Correlation between decline of WBCs in CSF and vancomycin minimum concentrations in CSF, 21 samples(r=0.609, p=0.003). One patient had no cerebrospinal fluid biochemical examination on sampling day.

DISCUSSION

The pharmacologic action of vancomycin is greatly dependent on CNS penetration which is affected by tissue distribution, and meningeal inflammation (4). To the best of our knowledge, this is the first study focused on the association between vancomycin penetration into CNS and clinical response in patients with postsurgical meningitis. Manufacturer recommended dose of vancomycin is 500 mg *iv* every 6 hours or 1000 mg *iv* every12 hours. In this study, 500 mg *iv* every 6 hours was used due to physicians' preference. Clinicians adjust dosage based on patients' creatinine clearance (CL_{cr}) or serum vancomycin concentrations. In this hospital, it is conventional that the first vancomycin concentrations in serum were monitored on day 3 or later, and in neurosurgery, lumbar punctures are done every other day or every other two days. Therefore, all samples was collected on day 3 or 4, in view of the clinical feasibility of sampling and samples were timely processed. In this study, the average time to process a lumbar puncture was on day 3. In addition, the combination of vancomycin plus ceftriaxone was used for patients with negative culture of CSF, to cover the major Gram-positive and Gram-negative strains.

In this study, one isolate of *S.Pneumoniae* (patient 2) was resistant to chloramphenicol and sulfamethoxazole/trimethoprim. This patient received ceftriaxone prior to enrolment to the study but did not show clinical improvement. This suggests that *S.Pneumoniae* was β-lactam resistant. Therefore, additional therapy of vancomycin was added to increase coverage. CNS infection due to *E.faecium* is rare. While in this study, patient 3, with persistent fever, headache, and lethargy, had a positive CSF culture for *E.faecium* which was only sensitive to vancomycin, teicoplanin and linezolid. This patient received vancomycin alone and clinical symptoms were improved after 7 days of vancomycin therapy and cure was achieved after 14 days of therapy. On day 3, this patient achieved a serum C_{min} of 15.73 mg/L, which reached the recommended target serum levels for meningitis (15-20 mg/L), but a relative low CSF C_{min} of 2.57 mg/L (13). According to the latest antimicrobial susceptibility surveillance of Gram-positive bacterial in China, the minimal inhibitory concentration (MIC) for vancomycin- sensitive *E.faecium* was 2 mg/L (5). Published pharmacokinetic- pharmacodynamic studies showed that vancomycin trough concentrations at 4-5 times the MIC best predicted clinical outcomes, and that vancomycin concentrations at 5-10 mg/L had maximum bactericidal activity in human CSF in vitro (3,14). Therefore, the CSF concentrations of 2.57 mg/L obtained in patient 3 might not be the optimal concentration, and higher CSF concentrations (8-10 mg/L) may have been needed to obtain a goal of four or five times above MIC to prevent the occurrence of vancomycin-intermediate or vancomycin- resistant *E.faecium*. The isolated *S.aureus*, *Coagulase-negative staphylococcus* and *S.saprophyticus* in this study were all resistant to cephalosporins and other β-lactam agents. Patient 13 had a CSF positive culture with *E.hirae*, which was Ciprofloxacin-intermediate sensitive and sensitive to vancomycin. Vancomycin was administered for 3 days, and patient had partial improvement of CSF indexes but headaches persisted. Subsequently lumbar drainage and combination therapy of meropenem 2 g *iv* every 8 hours was initiated.

Vancomycin has reported poor penetration into the uninflamed meningitis, with CSF concentrations of 0-3.45 mg/L and CSF to serum concentration ratio of 0-0.18 (4). Among patients with inflamed meningitis, vancomycin penetration into the CNS increased with CSF concentrations of 6.4-11.1 mg/L and CSF to serum concentration ratios of 0.36-0.48 (13). In this study, patients were given vancomycin as regular regimen of 500 mg *iv* every 6 hours, and the results showed that CSF C_{min} varied widely (ranging from 1.44 to 8.51 mg/L, with mean (±*SD*) of 3.63 ± 1.64 mg/L) and simultaneous CSF to serum

Table 1. Vancomycin C_{min} in CSF and serum, CSF-to-serum C_{min} ratio, and clinical response

Patient	Age(y)	Sex	Weight (kg)	Baseline Scr (μmol/L)	Baseline CLcr (mL/min)	CSF Cmin(mg/L)	Serum Cmin(mg/L)	CSF/serum ratio	Clinical response
1	74	M	65	70.2	74.5	2.97	16.9	0.176	Cured
*2	50	M	62	92.1	74.1	2.89	15.31	0.19	Cured
*3	58	M	71	151.4	47.0	2.57	15.73	0.163	Cured
*4	60	F	55	57.9	79.0	3.63	17.37	0.209	Improved
5	57	M	59	73.3	81.7	4.73	10.95	0.432	Cured
6	50	M	55	69	67.8	4.62	20.58	0.224	Improved
*7	55	M	60	67.3	92.6	4.57	13.71	0.333	Improved
8	62	F	No	51.4	No	4.29	11.29	0.38	Cured
*9	58	M	No	76.3	No	2.86	7.41	0.386	Cured
10	56	M	70	115.3	62.3	7.17	28.6	0.251	Improved
11	26	M	58	70.4	114.8	1.78	5.75	0.31	Cured
12	65	M	No	62.5	No	2.79	12.1	0.231	Improved
*13	55	M	77	78.8	101.5	4.03	7.07	0.57	Improved
14	51	M	No	73.2	No	2.78	11.77	0.236	Improved
15	46	M	No	56	No	2.99	15.48	0.193	Improved
16	60	M	No	63	No	4.01	8.19	0.49	Cured
17	25	F	55	50.9	129.1	1.44	5.07	0.284	Cured
18	48	F	58	61.2	90.6	2.37	11.84	0.201	Cured
19	62	F	50	64.6	62.7	8.51	17.18	0.495	Cured
20	53	F	53	40.5	118.3	2.56	11.56	0.221	Improved
21	30	F	46	37.7	118.6	2.94	13.3	0.221	Cured
22	57	F	63	69.8	77.8	3.35	17.15	0.195	Improved
Mean	52.6			70.58		3.63	13.38	0.291	
±*SD*	12.1			24.38		1.64	5.36	0.118	

*positive CSF cultures, patient 2, 3, 4, 7, 9, 13 had one isolate from positive CSF culture each, with *Pneumoniae streptococcus, Enterococcus faecium, Staphylococcus aureus, Coagulase- negative staphylococcus, Staphylococcus saprophyticus, and Enterococcus hirae*, respectively.

C_{min} ratio ranged from 0.163 to 0.570 (mean (±*SD*), 0.291 ± 0.118).Also, 12 patients achieved CSF C_{min} under 3.45 mg/L and 20 patients under 6.40 mg/L. In the 6 patients with positive CSF culture, the CSF C_{min} ranged from 2.57 to 4.57 mg/L and 50% (3/6) of these patients achieved CSF C_{min} under 3.45 mg/L. The results suggested that CNS penetration of vancomycin was limited and that partial patients with postsurgical meningitis might achieve sub-therapeutic CSF concentrations when the drug was given intravenously as regular regimen (500 mg, q6h). The results also indicated that this dose is perhaps inadequate for some patients. The variability of vancomycin penetrating the BBB is shown in some studies. CSF C_{min} of 1.6-11.1 mg/L, with a mean CSF to serum C_{min} ratio of 0.29 was reported in patients with bacterial meningitis (15). Patients with pneumococcal meningitis obtained CSF C_{min} of undetectable to 22.3 mg/L (6, 16). Another study showed that sufficient vancomycin C_{min} of 7.5 to 13.0 mg/L (*mean*, 11.2 mg/L) in CSF were obtained in 27 patients with acute community acquired meningitis after 3 days of treatment of vancomycin at a dose of 15 mg/kg every 12h (17). Various

vancomycin dosing including maintenance and loading dose, and administration methods such as intermittent or continuous infusion, different sampling times, and measurement methods of vancomycin concentrations might be explained for variations of vancomycin CSF concentrations in different studies. More importantly, vancomycin penetration into CNS correlates with the level and infectious process of inflammatory meningeal (7). Community acquired meningitis usually resulted in much more prominent damage of the blood brain barrier, which may explain the reason that CSF C_{min} in this study were clearly lower than that of another studies despite similar serum trough concentrations (16, 17). Moreover, the correlation between vancomycin CSF C_{min} and serum C_{min} was similar to other studies (14, 17).

The positive correlation between vancomycin CSF C_{min} and the decline of WBCs in the CSF after 3-5 days of therapy indicated that higher CSF C_{min} could be beneficial for improvement of WBCs in CSF. Surprisingly, the study failed to demonstrate an association between vancomycin CSF C_{min}, serum C_{min}, CSF to serum C_{min} ratio and clinical response. This indicates that perhaps monitoring CSF C_{min} would provide a better monitoring parameter. However, the results showed that higher CSF C_{min} and CSF to serum C_{min} ratio could not bring better clinical improvement, which might be related to the decline of subsequent CSF vancomycin concentrations as the BBB becoming more impermeable during prolong therapy (16). Paradoxically, some patients with improved clinical response had clearly low CSF C_{min}. Patients 11 and 17 had low CSF C_{min} 1.78 and 1.44 mg/L, respectively, which were far below the vancomycin CSF levels of 3.45 mg/L in inflamed meningitis, but both of them were cured which suggested that these patients may have causative pathogens with high susceptibility to vancomycin or have non-inflamed meningitis. While, patients 10 and 19 were clinically improved despite high CSF C_{min} (7.17 and 8.51 mg/L). Moreover, patients with similar CSF C_{min} obtained different clinical response such as patients 5, 6, 7, 8. Due to the negative CSF cultures and unobtainable antimicrobial susceptibility in all but 6 patients, it suggests that more post neurosurgery patients with reliable positive CSF cultures are needed to clarify the association between vancomycin concentrations and clinical response.

Infectious Diseases Society of America (IDSA) guidelines recommended maintaining vancomycin serum C_{min} between 15 and 20 mg/L for acute bacterial meningitis (18). In this study, 32% (7/22) patients achieved the target level, with widely various CSF C_{min} (ranging from 2.57 to 8.51 mg/L, mean ($\pm SD$) of 3.84±2.09 mg/L). Two patients obtained serum C_{min} over 20mg/L (patients 6 and 10, with CSF C_{min} 4.62, 7.17 mg/L respectively) without toxicity. No obvious improvement for clinical response of patients with higher serum C_{min} (≥15 mg/L) (p=0.666). More clinical data supporting a serum C_{min}≥ 15 mg/L for bacterial meningitis are needed. The IDSA recommended a vancomycin dosage of 15-20 mg/kg every 8-12h for acute bacterial meningitis (18). In this study, vancomycin was administrated as the regular regimen (500 mg *iv* every 6 hours). Also, the lowest patient weight in this study was 46 kg. By using 15 mg/kg/dose, this patient should have received 690 mg at minimum. The results suggest that the dosing regimen used in the hospital may not be the optimal to treat bacterial meningitis.

There was still some limitations for this study. The sample size of the study is small. Also, the inability to obtain reliable positive cultures in the hospital posed difficulties in determining true infection verses false negative cultures. The vancomycin dosing for postsurgical meningitis may not reflect current practice. Since vancomycin concentrations in this study were only obtained once, the relative stability of CSF concentrations during the therapy was unknown.

CONCLUSIONS

There was a positive correlation between serum C_{min} and CSF C_{min}. However, only CSF C_{min} was positively correlated with WBCs improvement. All other parameters such as CSF C_{min}, serum C_{min} and CSF to serum C_{min} ratio had no correlation with clinical response. Future studies with larger sample size are needed to determine the correlation between vancomycin BBB penetration or serum C_{min} and clinical response.

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