Effect of High-Volume Therapy on Cefazolin Serum Concentrations in Multiple-Trauma Patients

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Abstract

The aim of the study was to determine the effect of volume resuscitation on serum concentrations of cefazolin after severe multiple trauma: prospective and follow-up in a 6-bed trauma intensive care unit, university hospital (10 multiple trauma patients, injury severity score [ISS] > 17 patients).

Measurements of serum concentrations were done before, 0.5 and 4 hours after intravenous administration of 2 g cefazolin. The standard regimen of cefazolin administration was 2 g every eighth hour for 48 hours. The data are presented as median, minimum, maximum. Ten patients with an ISS of 29 (18 to 41) points and an age of 32 (22 to 77) years were included. The patients received a total of 9,700 (3,500 to 24,500) ml kristalloid solutions and median 3,800 (500 to 10,400) ml of blood and fresh frozen plasma on the day of the measurements. Before implementation of the measurements, all patients received a total dose of cefazolin between 4 and 10 g. Serum concentrations were 7 (6 to 27) mg/l immediately before start of the infusion (8 hours after the last administration), 186 (36 to 641) mg/l after 0.5 hours and 19 (11 to 60) mg/l at 4 hours after cessation of infusion. The serum concentrations did not correlate with the total doses of cefazolin given before implementation of the measurements.

The measured median serum concentrations of cefazolin after an interval of application of 8 hours were much lower than the needed minimum inhibitory serum concentrations against Staphylococcus (10 mg/l). To avoid low minimum serum concentrations and increase the efficacy of prophylactic antibiotic administration a shorter interval of application should probably be chosen.

Key Words

Cefazolin · Multiple trauma · Polytrauma · Antibiotic prophylaxis

Eur J Trauma 2000;26:74–80

Introduction

The routinely use of prophylactic antibiotic administration during fracture treatment is quite common. The beneficial effect of the prophylactic antibiotic administration was carried out in several studies, if antibiotics were given before skin incision [14, 20]. First-generation cephalosporins as cefazolin were most frequently used as prophylactic antibiotics, because they offered the best antimicrobiological activity against Staphylococcus strains, which were the most frequent bacterias in bone and soft tissue infections [13, 14, 20].

Several studies could demonstrate, that blood loss during standard operations probably affect serum and/or tissue concentrations. Therefore, an additional dose of cefazolin was recommended, if operation time exceeds 3 or 4 hours [1, 16, 21, 25, 26]. Patients with multiple trauma have often associated open or closed fractures and extended injuries to the soft tissue. Early stabilization of long-bone fractures in multiple-trauma patients was able to avoid organ dysfunction syndrome, pulmonary complications and to shorten the time of ventilation [4, 5]. If patients with single open ore closed fractures profit from prophylactic antibiotic administration, multiple-trauma patients could also benefit from

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Received: January 18, 2000; accepted: March 27, 2000.

prophylactic antibiotic administration to decrase the local infection rate.

Due to the traumatic shock after severe multiple trauma, blood loss and volume requirements significantly exceed to those of standard operations. The efficacy of prophylactic antibiotic treatment during early fracture fixation in multiple trauma might be limited due to the administration of large volumes of blood, plasma and kristalloid solutions. The purpose of this study was to demonstrate the effect of high-volume therapy on serum concentrations of cefazolin during the first 48 hours after trauma.

Patients and Methods

Ten multiple-trauma patients aged between 16 and 65 years and a minimum injury severity score (ISS) of more than 17 points were consecutively included. Local injury severity was scored according the abbreviated injury scale and injury severity in general was defined according the ISS [2, 3]. Patients with preexisting cardiac or infectious diseases were excluded from the study. The patients should be primarily admitted within 2 hours.

Single- or multiple organ failure syndrome (OF/MOF) were defined according to the MOF-score [12]. OF was diagnosed if the score of 1 organ or organ system received 2 points on more than 3 days. MOF was diagnosed if 2 or more organs failed on more than 3 days.

Sepsis was diagnosed by the definitions of the sepsis consensus conference [18]. A source of infection (positive blood culture) plus 2 or more of the following parameters:

1. 36 < temperature (° C) > 38,
2. 4,000 < leukocytes (ml) > 12,000 or immature neutrophils > 10%,
3. heart rate > 90 (min), and
4. respiratory rate > 20 (min) or P_{CO_2} < 32 mm Hg.

Pneumonia was diagnosed by the presence of 2 of the following criteria:

1. Purulent tracheal secretion with evidence of bacteria,
2. a new and persistent infiltration seen in the chest roentgenogram, and
3. a body-core-temperature > 38 °C [15].

Standard Treatment

Due to their injury severity, all patients were intubated and ventilated. Aspired mean arterial blood pressure was 70 mm Hg. Therefore, large volumes of kristalloid solutions and early administration of blood and plasma were part of the initial trauma management. Operations were timed due to their urgency and fractures of long bones were always stabilized during the first 8 hours. Thereafter, all trauma victims were treated at the trauma intensive care unit. Erythrocyte sediments and fresh frozen plasma were given 1:1 to increase the hemoglobin concentration (10 g/l) and to normalize the coagulation cascade. Albumin, hydroxyethyl starch or dextran were not infused during the whole ICU-treatment. All patients received dopamine (0.15 mg/kg/h) to support kidney function. If extensive volume substitution could not stabilize the cardiovascular system, catecholamines were given.

Cefazolin Administration and Measurements

The standard regimen was the administration of 2 g of cefazolin every eighth hour for at least 48 hours. The first dose of cefazolin was given during the initial resuscitation phase before the beginning of operations, within 2 hours after trauma. The measurements of the serum concentrations were initiated after a minimum dosage of 2 times 2 g of cefazolin. It was assumed, that a minimum of 2 doses of cefazolin were necessary to achieve a steady state. Serum concentration of cefazolin was measured immediately before the next dose was given. Serum concentrations were also measured 0.5 hours and 4 hours after finishing of the infusion. 10 ml of blood were collected in a special serum syringe under sterile conditions, centrifuged for 10 minutes and stored at -70 °C. The complete set of samples was shiped to a drug laboratorium and analyzed by using the high performance liquid chromatography method (Laboratorium: J. Enzenauer, A. Wilhelm, M. Bringemeier, Osnabrück, Germany) [10].

Statistics

The data indicated in the results are presented as median, minimum and maximum. The correlation between the variables "given dose of cefazolin before measurements", "total liquid volume administration", and "serum concentrations of cefazolin at 0 hour" was also tested (Pearson, 2-sided, $p < 0.05$). All calculations were performed using programs of the Statistical Package for the Social Sciences (SPSS for Windows 7.5.2, SPSS Inc.).

Results

Ten patients (9 men, 1 woman) were included in this prospective evaluation. Median ISS was 29 (18 to 41) points. The median age was 32 (22 to 77) years, the body weight was 75 (60 to 118) kg and the body surface area was 1.95 (1.68 to 2.50) m^2 (Table 1). The kidney function was regular and median kreatinine concentration was 0,85 (0.4 to 1.1) mg/dl (Table 1).

The first dose of cefazolin was applicated during the resuscitation in the emergency room, within 2 hours after trauma. All patients received a minimum dose of cefazolin of 2 times 2 g to avoid falsely low serum concentrations due to a lacking steady state. The serum concentrations of cefazolin from 3 patients were measured before the third dose was given (16 hours after trauma). In 4 cases, serum concentrations of cefazolin were measured after administration of 3 times of 2 g cefazolin (24 hours after trauma) before the fourth dosage was given. In 3 more cases serum concentration of cefazolin were measured after a total dose of 5 times of 2 g cefazolin (32 hours after trauma) before the last dose of cefazolin was administered. Adjusted for body weight the median dose of cefazolin was 27 (17 to 33) mg/kg and adjusted for surface area the median dose was 1,026 (800 to 1,190) mg/m^2. During application no adverse or side effects occurred (Table 2).

Patient	Sex	Age (years)	ISS	Ventilation	ICU	OF/MOF	Sepsis	Pneumonia	Local complications	Local bacteria
1	m	23	25	47	63	Liver, cardiovascular	Yes	Yes	Pelvis osteomyelitis	S. aureus
2	m	42	29	36	40	No	No	Yes	Calcaneus osteomyelitis	S. aureus
3	m	34	22	5	6	No	No	No	No	–
4	m	27	27	22	24	No	No	Yes	No	–
5	m	33	18	21	22	Cardiovascular	No	Yes	No	–
6	m	22	36	23	25	Liver	Yes	Yes	No	–
7	f	77	29	120	131	Cardiovascular, liver	Yes	Yes	No	–
8	m	30	41	27	34	Lung, liver, cardiovascular	No	No	Infected hematoma	S. epidermidis
9	m	46	34	42	49	No	Yes	Yes	No	–
10	m	29	29	23	25	Liver, cardiovascular	Yes	Yes	No	–

Table 1
General description of the included patients. ISS = injury severity score; Ventilation = days from trauma to extubation; ICU = days from trauma to discharge from the ICU; OF/MOF = single/multiple organ failure.

Patient	Dose (mg/kg)	Dose (mg/m^2)	Total dose (g)	Kristalloids (ml)	Blood+ffp (ml)	0 hour (mg/l)	0.5 hours (mg/l)	4 hours (mg/l)
1	19	889	10	13,000	5,800	20	58	27
2	8	1,042	6	7,400	2,800	12	36	30
3	29	1,074	4	3,500	900	11	201	17
4	29	1,053	10	7,300	4,300	7	514	14
5	17	800	6	21,500	5,000	7	171	22
6	33	1,149	6	12,000	3,000	7	230	19
7	32	1,190	4	7,300	10,400	27	641	60
8	21	909	10	14,700	3,300	6	46	11
9	26	1,010	6	7,000	4,400	6	286	19
10	20	889	4	15,000	2,000	7	113	11

Table 2
Dose and serum concentrations of cefazolin. Dose (mg/kg) = cefazolin dose adjusted for body weight; Dose (mg/m^2) = cefazolin dose adjusted for body surface area; Total dose (g) = given total dose of cefazolin before implementation of the measurements; Kristalloids (ml) = total given volume of kristalloid solution; Blood+ffp (ml) = given total volume erythrocyte sediments and fresh frozen plasma; 0 hour (mg/l) = serum concentration of cefazolin before the next dose was given; 0.5 hours (mg/l) = serum concentration of cefazolin at 0.5 hours after administration; 4 hours (mg/l) = serum concentration of cefazolin 4 hours after administration.

On the day of the cefazolin application a median of 9,700 (3,500 to 21,500) ml of kristalloid solutions and a median of 3,800 (900 to 10,400) ml of blood and fresh frozen plasma were administered. The median of the total given fluid volume on the day of application was 10,275 (4,400 to 26,500) ml (Table 2). The median serum concentrations of cefazolin of all measurements were 7 (6 to 27) mg/l immediately before start of the infusion (or 8 hours after the last administration), 186 (36 to 641) mg/l after 0.5 hours and 19 (11 to 60) mg/l at 4 hours after cessation of infusion (Figure 1). After a given dose of 2 times 2 g of cefazolin, the median serum concentrations before the next application was 11 (7 to 27) mg/l, 201 (113 to 641) mg/l after 0.5 hours, and 17 (11 to 60) mg/l at 4 hours after cessation of infusion. After a given dose of 3 times 2 g cefazolin the median serum concentration before the next dosage was 7 (6 to 12) mg/l, 201 (36 to 286) mg/l after 0.5 hours, and 21 (19 to 30) mg/l after 4 hours. After a given dose of 5 times 2 g cefazolin, the median serum concentrations were 7 (6 to 20) mg/l before the next administration, 58 (46 to 514) mg/l after 0.5 hours and 14 (11 to 27) mg/l 4 hours after cessation of the infusion. The given dose of cefazolin given before the measurements did not correlate with the amount of the serum concentrations at 0 hour (Figure 2). There was also no statistically significant correlation between the measured serum concentrations of cefazolin at 0 hour and the administered total liquid volume (Figure 3).

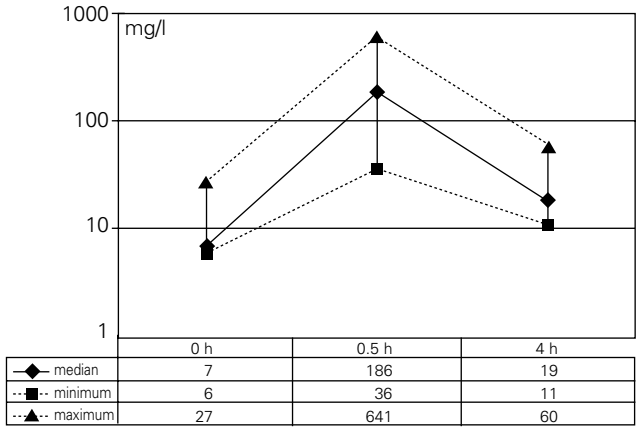

Figure 1
The figure presents median, minimum and maximum serum concentrations at 0 hour (or 8 hours after the last administration), at 0.5 hours and at 4 hours after administration of 2 g cefazolin for all patients. Median concentrations after 4 hours and 0 hour were lower than reported in the literature [10, 11, 26].

Three patients developed local complications. One patient developed osteomyelitis of the pelvis. This patient had a closed unstable dislocated fracture of the pelvis with massive bleeding in the retroperitoneum, which was treated with external fixation. The infection occurred after 14 days, and was caused by Staphylococcus aureus. Another patient developed osteomyeli-

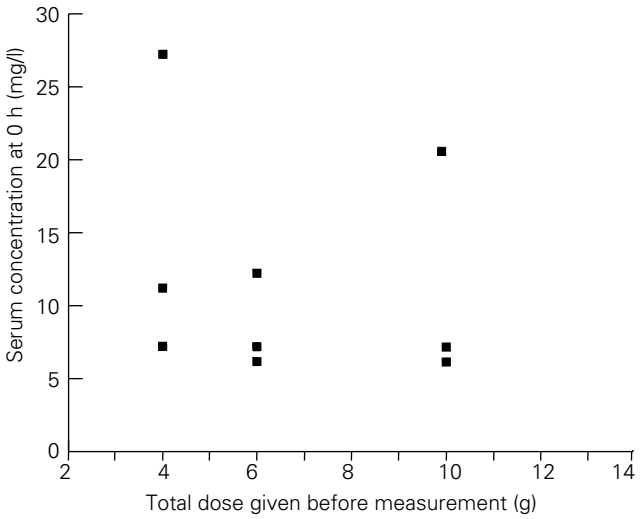

Figure 2
This figure shows the correlation between the serum concentration at 0 hours (8 hours after last dosage) and the total given dose of cefazolin before initiation of the measurement. A correlation between the variables could not be observed.

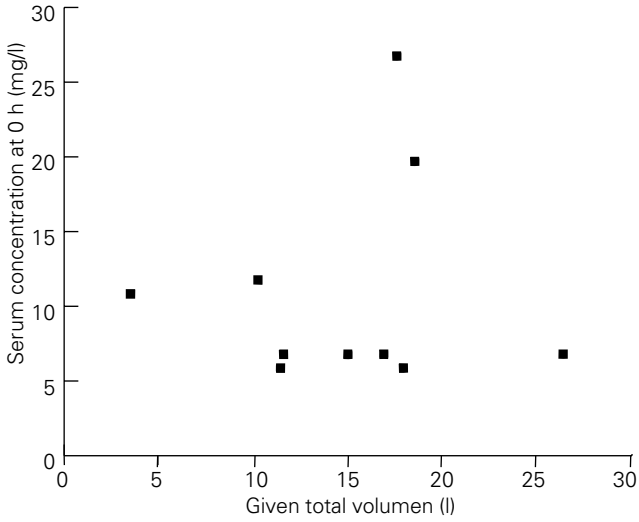

Figure 3
This figure demonstrates the correlation between the given total volume (kristalloids, blood, fresh frozen plasma) and ther serum concentrations of cefazolin at 0 hour. Obviously there was no correlation between the tested variables.

tis of the calcaneus. It was a closed comminuted fracture of the calcaneus and the distal tibia, which was initially treated by external fixation. Infection occurred 14 days after initial operations (8 days after definitive fixation by plate osteosynthesis of the calcaneus and was also caused by Staphylococcus aureus. One more patient developed an infected hematoma at the back, which was caused by an extensive skin contusion and a fracture of the thoracic spine. The spine fracture was treated non-operatively, but the deglovement was treated by insertion of suction drainages. Four days after removement of the drainages the patient showed local signs of infection. During operation an infected hematoma (no abscess) was removed and treated successfully with suction drainages again. No patient died during the hospital stay. Ventilator treatment was necessary for a median of 25 (5 to 120) days and median stay on the intensive care unit was 30 (6 to 131) days (Table 1).

Discussion

The prophylactic antibiotic treatment is commonly used, if postoperative infection would have serious consequences on the outcome of surgery [14]. Preoperative antibiotics could reduce local infections in case of stabilization of fractures or during total hip replacement, but not avoid systemic infections [13, 14]. Cefazolin a first-generation cephalosporin is frequently used in orthopedic surgery because cefazolin (and other first-generation cephalosporins) offers the best activity against gram-positive, but less against gram-negative bacteria. One of the most important complications during clean orthopedic surgery is the development of osteomyelitis, which is mainly caused by Staphylococcus.

Advantages of cefazolin compared to other first-generation cephalosporins were seen in the high protein binding rate, which increases half-time and prolonges antibiotic effects [8, 9, 11, 23]. The elimination half-lives of cefazolin during standard operations were found to be between 90 and 120 minutes [10, 26]. The antibiotics had to be given at least 30 minutes before skin incision to achieve sufficient serum concentrations of cefazolin, because low serum, tissue or bone concentrations may be able to promote a bacteria resistance [13, 14]. If prophylactic antibiotic treatment is recommended in patients with single closed or open fractures, then multiple trauma patients with fractures and soft tissue injuries should also receive prophylactic antibiotics.

The median serum concentrations 30 minutes and 4 hours after cessation of the infusion were comparable with measurements of other authors [10, 11, 17]. DiPiro et al. [10, 11] found a strong correlation between serum concentration and time and a weak correlation between free cefazolin serum concentration and muscle concentration. Cephalosporins have no postantibiotic effect like aminoglycosides [22]. In contrast to aminoglycosides, the antibiotic of cephalosporins is not dependent to the peak level, but it is dependent to a constant plateau concentration, which should be the 10-fold of the MIC_{90} [24]. The repetitive intravenous application of cefazolin was considered to cause sufficient serum concentrations by most authors, but others prefered continuously intravenous infusion [6, 7].

It was found, that blood loss during standard operations could alter the serum concentrations of cefazolin and tissue concentrations [8–11, 16, 21, 23, 25, 26]. According to the aspect of low tissue and especially bone concentration a further dose of cefazolin after 2 or 3 hours was recommended [7, 8]. Despite these studies, the influence of blood loss and volume therapy on cefazolin serum concentration was not investigated in multiple trauma patients. In case of severe multiple trauma blood loss exceeds to those in simple fractures and causes in shock. To avoid the complications due to the traumatic shock, standard treatment includes the administration of large amounts of kristalloid solutions, blood and fresh frozen plasma to stabilize circulation and increase coagulation. During standard operations with exceeding blood loss up to 1,600 ml and a given total volume of up to 5,000 ml a strong correlation between blood loss and serum concentration of cefazolin was observed during an observation period of 300 minutes [26]. In case of multiple trauma the amount of fluid administration exceeds over those during standard operations and the duration of fluid administration was much longer. Otherwise the fluid administration differed between the observed patients because of injury severity, duration of shock and catecholamin support. Loss of albumin and other proteins as well could decrease the distribution volume of cefazolin. Due to these considerations the elimination half-times of cefazolin could be higher than assumed.

During high-volume resuscitation, 2 g of cefazolin resulted in serum concentrations of minimum 19 mg/l at 4 hours and 7 mg/l at 8 hours after administration. The

minimum inhibitory concentration MIC_{90} of cefazolin was found to be 0.5 to 2 mg/l for Staphylococcus, 8 to 32 mg/l for Streptococcus, 2 to 4 mg/l for Escherichia coli, 1 to 2 mg/l for Klebsiella and 8 to 100 mg/l for several strains of Proteus in vitro. The plasma and tissue concentrations of cefazolin should have been more than 2- to 5-fold the MIC_{90} during the whole period to avoid local infections [6, 7, 9]. However, the high protein binding rate (80 to 86%) leads to much lower effective serum concentrations [7, 9–11]. Bleeding and the increase of vascular permeability caused in a decrease of the serum concentrations of proteins like albumin and might support a decrease of the serum concentrations of cefazolin. These lower effective concentrations also result in lower tissue and bone concentrations [9, 11, 13, 22, 27]. Therefore bone and tissue concentrations were found to be 10 to 30% of the measured serum concentrations [9–11]. With regard to our measurements, the tissue and bone concentrations were lower than the required MIC_{90} for all gram-positive bacterias including Staphylococcus. The approximated but not measured tissue or bone concentrations were estimated 1.9 to 5.7 mg/l (4 hours) or 0.7 to 2.1 mg/l (8 hours) for our group of patients. Despite the prophylactic antibiotic treatment 3 local infections occurred. The osteomyelitis on the calcaneus of patient 2 was probably caused by the second operation, which also was performed with antibiotic prophylaxis. There was no beneficial effect of cefazolin on the development of systemic infections or pneumonia [14].

The results of this study may be limited because of lacking tissue and bone concentrations but several studies could demonstrate a direct dependency between serum concentrations and tissue or bone concentrations [6, 9, 11, 13, 25, 27]. With regard to these studies and to avoid local complications (i. e. bleeding, infection), we waived to measure tissue and bone concentrations. Another limitation may be the different total dosis of cefazolin administered before initiation of the measurements. This could be excluded due to a missing correlation between the given total dose cefazolin before the measurements and the serum concentration at 0 hour. The steady state could be observed after 2 times 2 g cefazolin and was not altered by any additional dose cefazolin.

In conclusion, a dosage of 2 g cefazolin every eighth hour was not able to achieve sufficient serum concentrations in case of high-volume resuscitation after multiple trauma. This decrease of the measured serum concentration below the needed minimum inhibitory serum concentration diminishes the efficacy of prophylactic antibiotic administration. In case of standard operations a re-dosage of 2 g of cefazolin after 3 hours was recommended. According to this recommendations, a shorter interval of application should be preferred. Up to now, it is not proven that application of 2 g of cefazolin in shorter intervals (every fourth or sixth hour) could achieve higher serum concentrations and benefit the patients. A further study should be performed to clarify these questions.

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