Effect of Severity Disease on the Pharmacokinetics of Cefuroxime in Children with Multiple Organ System Failure

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The aim of the present study was to investigate if the severity of illness affected the pharmacokinetics of cefuroxime in 11 children diagnosed with multiple organ system failure. The patients were assigned to a severely ill group (group 1), a very severely ill group (group 2), or a control group (group 0). Blood samples were taken and cefuroxime concentrations were measured in plasma by HPLC after the first intravenous infusion of 100 mg of cefuroxime per kg of body weight. The pharmacokinetic profile of cefuroxime exhibited both one and two compartmental distribution. Statistically significant differences between the pharmacokinetic parameters of the severe (group 1) and the very severe patients (group 2) were found, and significant differences ($p < 0.05$) in the pharmacokinetic parameters between groups 1 and 2 vs. the control group were observed for most of the parameters analyzed. However, there was no statistical difference in clearance between group 1 and the control group. The data indicate that the pharmacokinetic differences determined by severity of disease are useful for establishing an individualized regimen dosage in children with multiple organ system failure.

Key words antibiotic; child; pharmacokinetics; cefuroxime

Cefuroxime (CXM) is a second generation cephalosporin antibiotic that is active against Gram-positive and Gram-negative bacteria^{1,2)} and is a cephalosporin with enhanced β -lactamase resistance.³⁾ The pharmacokinetics of CXM has been studied in healthy volunteers,⁴⁾ in infants and children with bacterial meningitis,^{5,6)} as well as in patients with pneumonia.^{6,7)} On the other hand, the pharmacokinetics of CXM has been studied in normal subjects and in those with impaired renal function,⁸⁾ and the results suggested that no drug accumulation occurs in patients with normal or mildly impaired renal function if CXM is administered at 6-h intervals. However, in patients with severe uremia, drug levels are likely to accumulate in serum until they reach levels of about 6- to 7-fold the initial values after 3 days of repeated dosing. The magnitude of drug accumulation is dependent upon the dose administered and the level of the patient's renal function. In such patients the dosage interval should be extended to 24 h. Nevertheless, its pharmacokinetic characteristics have not been studied in children diagnosed with multiple organ failure, in whom the effect of the severity of illness could affect the pharmacokinetics of this drug and consequently its therapeutic effectiveness.⁹⁾ It is well known also that factors different to the ones described above can modify the pharmacokinetic profiles of specific populations.¹⁰⁾

In the present study, we evaluated the severity of multiple organ system failure and sepsis on the CXM pharmacokinetic parameters that may be of therapeutic value.

MATERIALS AND METHODS

Subjects The population under study consisted of 11 pediatric patients (4 males and 7 females) ranging in age from 4 months to 14 years (median of 1 year 5 months). Body weight ranged from 5.1 to 45.0 kg, with a median of 8.2 kg. All of the subjects were hospitalized in the intensive care unit

of the National Institute of Pediatrics in Mexico City and were diagnosed with multiple organ system failure (MOSF). MOSF is defined as the failure of at least two body systems and it takes into consideration the status of several different systems such as cardiovascular, respiratory, central nervous, renal and hepatic systems.¹¹⁾

Physical examination and laboratory tests before the study were undertaken for each patient: hemoglobin concentration, total protein, serum albumin, serum glutamic oxaloacetic transaminase (SGOT) and glutamic pyruvic transaminase (SGPT), urea and creatinine to determine hepatic and renal function (Table 1). The subjects were divided in two groups according to the criteria of the National Institute of Pediatrics of México City based on the severity of illness: Group 1 (5 subjects, 4 months to 1 year 11 months of age, and from 5.95 to 10.1 kg of weight) who were classified as severe but who did not require intubation, and Group 2 (6 subjects, 6 months to 14 years old, weighting 5.1 to 45 kg) classified as very severe, who required intubation. We included a control group consisting of 4 pediatric patients (2 males and 2 females) aged 5 to 11 years old (median 8 years old) and weighing between 16 and 40 kg (median 27.5 kg) diagnosed with pharyngoamygdalitis and who were treated with CXM and considered to be not severely ill.

The protocol for the study was approved by the Ethics Committee of the National Institute of Pediatrics of Mexico. Informed consent was obtained from the parents or guardians of the subjects.

Pharmacokinetic Study In all pediatric patients, cefuroxime (Zinacef, Glaxo[®]) was indicated as part of their treatment for septicemia or septic shock, for 14 d at a dose of 100 mg per kg of body weight, administered every 6 h by intravenous infusion for 30 min.

The CXM concentrations in plasma were measured after the first intravenous dose of CXM on the first day of the ther-

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Table 1. Clinical Characteristics of Study Patients

Patient/ gender	Age (month)	Weight (kg)	Hb (gr %)	Total proteins (gr %)	Albumin (gr)	SGOT ($\mu\text{g/ml}$)	SGPT ($\mu\text{g/ml}$)	Urea (mg/dl)	Creatinine (mg %)
1/F	23	10.1	15.8	5.9	3.0	221	49	32.1	0.3
2/F	6	5.9	14.6	5.1	3.1	18	17	10.7	0.26
3/F	7	5.5	13.0	5.2	3.3	22	13	26	0.20
4/M	18	8.2	13.0	6.3	4.3	4	2	2.1	0.13
5/M	168	45.0	14.0	8.4	3.2	16	13	19	0.7
6/F	15	6.6	10.9	7.0	3.4	17	14	6.4	0.49
7/F	108	21.1	13.0	5.7	3.2	21	23	19.0	0.5
8/M	36	11.0	13.3	5.9	3.4	23	28	12.8	0.2
9/F	17	9.1	10.3	6.1	3.3	19	16	44.9	0.84
10/F	6	5.1	8.6	5.1	3.1	119	65	23.5	0.34
11/M	4	6.0	13.9	6.1	3.2	93	84	33	0.5

Patients 1, 2, 6, 9 and 11 are severely ill group. Patients 3, 4, 5, 7, 8 and 10 are very severely ill group.

apy. The control subjects received the same dose of CXM infused over a 30 min period, using an infusion pump.

Blood samples were collected through an intravenous catheter in the arm at 5, 15, 30, 45 and 60 min, and 2, 4, 5, 6, 7 and 8 h after the infusion delayed for 2 h only for the next dose. Samples were placed in heparinized tubes and centrifuged at 800 *g* for 10 min to obtain plasma and then stored at -20°C until assayed.

Analytical Method Concentrations of CXM in plasma were determined by a modified high pressure liquid chromatography method (HPLC) previously described by Nilsson-Ehle I,¹²⁾ which modifies the ratio of the mobile phase consisting of acetic acid/water/methanol (1:69:30 by vol). To 0.5 ml of plasma, 1 ml of dimethylformamide was added and then the mixture stirred rapidly on a vortex-type mixer before being heated for 1 min in a water bath set at 60°C . After centrifugation at 400 *g* for 10 min, an equal volume of distilled water was used to facilitate the subsequent passage through 0.6 μm filters (Millipore Corp.).

A 40 μl aliquot of the filtered solution was injected into a liquid chromatography system consisting of a Waters model U6K injector valve, pump model M45, and absorption detector model 440. The column used was a C 18 μ -Bondapak (5 μm , 150 $\times$ 3.9 mm I.D.) and the mobile phase was filtered and degassed acetic acid/water/methanol. The flow rate of the mobile phase through the HPLC system was 1.5 ml/min. The area was plotted by a Waters Millipore data module. Linearity was assessed in the range of 10–1000 $\mu\text{g/ml}$ resulting less than 7% and the mean extraction recovery was 100.9%. The limit of detection was 0.5 $\mu\text{g/ml}$. The standard curve was linear ($r^2 > 0.99$) within the range of concentrations. Inter- and intraday variation coefficients of CXM were 5.9% and 9.3%, respectively.

Pharmacokinetic Analysis Profiles of decline curves were plotted for CXM plasma concentration against time for each patient studied, and the experimental data were fitted to a monoexponential function of the form of Eq. 1, or a biexponential function of the form for Eq. 2¹³⁾ as follows:

$$C_p = C_p^0 e^{-kt} \quad (1)$$

$$C_p = A e^{-\alpha t} + B e^{-\beta t} \quad (2)$$

For the monoexponential model Eq. 1 is applied, where C_p is the concentration of CXM in plasma at time t post-dosing, C_p^0 is the concentration at time zero, and k is the elimination constant. For the biexponential model, A and B are concen-

tration coefficients, and α and β are respectively the rate constants governing the fast and slow phases of drug loss from plasma.

Plasma concentration–time curves were analyzed using NONLIN least square regression software and the parameter estimates were obtained by WINNONLIN version 1.1,¹⁴⁾ which applies the AKAIKE criteria for selection of the best compartmental model. All concentrations of CXM were weighted according to their reciprocals during the computer analysis.

Statistical Analysis Data were analyzed by ANOVA, and for dispersion of the data the nonparametric Mann–Whitney U test was used.¹⁵⁾ The difference is whether the data can be assumed to be normally distributed or not. A p value < 0.05 was considered statistically significant.

RESULTS

The clinical diagnoses for the study patients are listed in Table 2. The cause of the disease severity was generally multifactorial and included MOSF, septicemia and septic shock. Figure 1 shows the profile of the plasma concentration–time curves for each patient. In 2 of 5 patients whose illnesses were classified as severe (Group 1) (curves 9 and 11), the curves for plasma concentrations vs. time for CXM were best defined by a one-compartment open pharmacokinetic model. In the other 3 subjects (curves 1, 2, 6), the curves were best explained by the biexponential model. The pharmacokinetic profiles for the very severe patients (Group 2) are shown in Fig. 2. In 5 of 6 patients, the decline in drug levels was biphasic and was explained by a two-compartment open model. In the remaining patient (curve 10), the curve was characterized by a monoexponential model.

The pharmacokinetics parameters, expressed as the median and range, are shown in Table 3. With respect to α , there were no significant differences when group 1 and group 2 were compared, although significant differences were observed compared to the control group.

With respect to β , the decreases were as follows: for group 1, severely ill patients, 0.2 (0.1–0.6 h^{-1}) and group 2, very severely ill patients 0.1 (0.04–1.4 h^{-1}), compared to the control group 0.08 (0.04–0.1 h^{-1}), there were statistically significant differences between the severe group and very severe group with respect to the control group, $p = 0.001$ and $p = 0.05$, respectively.

Table 2. Diagnoses of the Study Patients

Patient number	Clinical diagnosis	Classification disease
1	Fulminant hepatitis, seizures, hepatic encephalopathy, septicemia, cerebral edema, pneumonia	Severe ^{a)}
2	Septicemia, chicken pox, atopic dermatitis	Severe
6	Congenital hydrocephalus, valvular dysfunction by distal infection, septicemia	Severe
9	Acute gastroenteritis, dehydration, neuroinfection by <i>H. influenzae</i> , septicemia	Severe
11	Septicemia, seizures, anemia, acute gastroenteritis, respiratory tract infection	Severe
3	Bacterial meningitis <i>H. influenzae</i> , septicemia, cyanotic congenital heart disease, seizures, pneumonia	Very severe ^{b)}
4	Meningitis by <i>H. influenzae</i> , septicemia, seizures, congenital hydrocephalus, frontal hygroma	Very severe
5	Neuroinfection by klebsiella, septic shock, congenital hydrocephalus, seizures	Very severe
7	Septicemia, chicken pox, pneumonia, heart failure, hypoxia	Very severe
8	Septic shock, seizures, septic arthritis, second degree burn	Very severe
10	Pneumonia, cyanotic congenital heart disease, heart failure, hypoxia, seizures	Very severe

a) Severe, patients who did not require intubation, b) Very severe, those who required intubation. According to the criteria of the National Institute of Pediatrics of México.

Fig. 1. Pharmacokinetic Profile of Cefuroxime in Group 1 (Severely Ill Children)

Axes represent plasma levels vs. time after infusion.

The elimination half life ($t_{1/2}$) was longer in group 2 (1.3 h, range, 0.08 to 1.9 h) than in group 1 (1.0 h, range, 0.1 to 1.4 h) and the control group (0.5 h, range, 0.2 to 1.1 h). Statistical differences ($p=0.05$) were observed between groups. The apparent volume of distribution, V_d , of CXM was 1.6 l/kg (1.0 to 4.0 l/kg) in group 1, 1.5 l/kg (0.9 to 1.8 l/kg) in the control group, and 3.1 l/kg (0.9 to 9.5 l/kg) in group 2. In the value corresponding to the area under the curve (AUC), there were statistically significant differences between the three groups analyzed, i.e., the very severe group vs. the severely ill group ($p=0.02$), group 2 vs. the control group ($p=0.01$), and the severely ill group vs. the control group ($p=0.02$).

Significant differences in clearance (Cl_t) were found between the very severely ill (group 2) patients (1.87, range, 0.25 to 0.77 l/kg/h) versus the severely ill (group 1) patients (0.48, range, 0.26 to 1.96 l/kg/h) ($p=0.03$) and between group 2 and the control group (0.55, range, 0.10 to 0.96 l/kg/h) ($p=0.02$). However, there was no statistically

significant difference in Cl_t between group 1 and the control group.

DISCUSSION

The patients were stratified as severely ill or very severely ill according to the criteria established by the National Institute of Pediatrics based on whether or not they required intubation. The severity of illness in the children under study resulted in statistically significant changes for most of the pharmacokinetic parameters of CXM. Such variations were more evident in the value of the elimination constant and consequently other parameters such as V_d , AUC and Cl_t for children classified as very severely ill due to MOSF.

Critically ill patients constitute a unique challenge in drug dosage due to physiological alterations that accompany severe illness and the changing condition of these patients.

Knowledge of the pharmacokinetic implications of physiological changes in critically ill patients and the impact on

Fig. 2. Pharmacokinetic Profile of Cefuroxime in Group 2 (Very Severely Ill Children)

Axes represent plasma levels vs. time after infusion.

Table 3. Pharmacokinetic Parameters of the Patients in the Severe, Very Severe and Control Groups

Parameters	Control patients	Group 1: severe patients	Group 2: very severe patients
α (h^{-1})	1.0 (0.4—2.5)	2.2 (1.4—3.9)	2.0 (0.3—9.1)
β (h^{-1})	0.08 (0.04—0.1)	0.2 (0.1—0.6)	0.1 (0.04—1.4)
$t_{1/2}$ (h)	0.5 (0.2—1.1)	1.0 (0.1—1.4)	1.3 (0.08—1.9)
Vd (l/kg)	1.5 (0.9—1.8)	1.6 (1.0—4.0)	3.1 (0.9—9.5)
AUC ($\mu\text{g}/\text{ml}/\text{h}$)	116.4 (84.9—161.7)	121.6 (59.6—202.1)	190.7 (79.6—729.7)
Cl _t (l/kg/h)	0.55 (0.10—0.96)	0.48 (0.26—1.96)	1.87 (0.25—0.77)

Data are presented as the median (minimum value and maximum value). α and β are the rate constants for fast and slow phases of drug loss from plasma, respectively, AUC: area under curve, Vd: volume of distribution, Cl_t: clearance.

pharmacodynamics is useful for selecting an initial dosage regimen and for further drug dosage adjustments.

Intraindividual variations due to sepsis^{16,17)} and mechanical ventilation^{18,19)} have been recently described although not extensively evaluated. Changes in cardiac output, renal and hepatic function,²⁰⁾ and circulating serum proteins, commonly seen in critically ill septic patients,^{16,21)} can alter the rate of drug elimination and consequently its plasma levels. It is widely accepted that many patients with sepsis show extravascular fluid sequestrations, resulting in substantial intravascular volume depletion. Since CXM is a drug that distributes throughout the body water in severely ill patients,²²⁾ where hemodynamic changes occur, it is probable that this drug fails to exert its antimicrobial effectiveness.

Our results indicate that the level of illness severity in patients diagnosed with MOSF showed great variations in the pharmacokinetic parameters of CXM, and these results involve wide variations that must be considered when preparing an individualized dosage. Based on the pharmacokinetic differences found in this study regarding the action of CXM, there is a need to make an adjustment in the maintenance doses of this antibiotic according to the severity of the dis-

ease.

The elimination of this drug followed a biexponential profile due to the existence of a second compartment, inducing a slow terminal elimination phase with clinical consequences with respect to its pharmacological effect, as in the case of the severity of illness. The Vd was observed to be greater in patients classified as very severely ill, which is augmented because most of them presented with sepsis, whose percentage of body weight corresponds to water, thus contributing to an expansion of extravascular fluid volume and increasing the apparent Vd of CXM. Similar conclusions that agree with our findings were reported by Marik²³⁾ and van Dalen and Vree.²⁴⁾ Both studies reported that Vd was increased in those patients, and even recommended that such patients should receive larger loading doses of the antibiotic in order to achieve therapeutic blood levels rapidly. The Vd of the antibiotic may be useful in determining the degree of capillary leak and tissue oedema that accompanies sepsis. The loss of venomotor tone during sepsis, with increased peripheral venous pooling, are additional factors which promote the redistribution of fluid and cause an expansion of extracellular fluid. In this respect, rapid disappearance from plasma into

the expanded extravascular fluid volume, commonly seen in septic patients, is a physiological explanation with greater support.²⁵⁾ Most likely the recently described atrial natriuretic peptide regulating water and salt homeostasis plays an important role in the distribution of water-soluble drugs by shifting fluid between the extra- and intravascular compartments during sepsis and hypoperfusion situations due to the existence of decreased peripheral resistance.^{26,27)} This kind of patient generally presents with a certain degree of malnutrition, which leads to decreased protein levels. However, the amount of drug binding to protein has an influence on the Vd so decreased protein levels will result in an increased Vd.

In summary, our finding regarding an increase in Vd, and prolonged elimination constant in very severely ill patients implies that larger loading doses are required to achieve peak therapeutic levels during the initial therapy and subsequent adjustment of maintenance doses, due to the slower rate of elimination of CXM.

However, as critically ill patients suffer continuous hemodynamic, renal and respiratory changes, it seems advisable to closely monitor the plasma levels of CXM throughout therapy, thus improving patient outcome using pharmacokinetic management and individualized pharmacokinetic dosing.

It is concluded that to understand the pharmacokinetics of CXM in critically ill infants and children, it is necessary to administer an adequate antimicrobial treatment, which contributes to attaining an effective pharmacologic response. The present work may be helpful in carrying out rational drug use, based on individual changes in the pharmacokinetics of CXM, which constitutes an essential tool in the management of critically ill children.

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