The pharmacokinetics of nifurtimox in chronic renal failure

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Summary. The pharmacokinetics of nifurtimox, a drug used in the treatment of *Trypanosoma cruzi* infections, has been studied in seven patients with chronic renal failure undergoing haemodialysis, and in seven healthy subjects.

Each subject took nifurtimox 15 mg · kg^{-1} orally and blood samples were obtained for 10 h after administration. Nifurtimox in serum was analyzed by HPLC.

The patients with chronic renal failure had a higher C_{max} than the control subjects due to a change in systemic availability. An alternative explanation would be that both the distribution volume and the clearance had changed.

The mean half-life in the patients with chronic renal failure was similar to that in the healthy subjects.

Key words: Nifurtimox, Chagas' disease; renal failure, pharmacokinetics

Chagas' disease is a parasitic infection caused by *Trypanosoma cruzi*. The high morbidity and mortality from Chagas' disease raise very important health, social and economic problems in Latin-American countries [1]. In the temperate zone of Chile, Chagas' disease has endemic-enzootic characteristics, with both rural and suburban distributions. The prevalence of human infection is estimated to be 15% [2].

Nifurtimox (Fig. 1) is a substituted nitrofuran compound that has been used in the treatment of *Trypanosoma cruzi* infections. It is effective in eradicating the amastigote and epimastigote forms of the parasite, and the reproductive forms are even more sensitive to its action. The minimum inhibitory concentration *in vitro* is 1 μmol · l^{-1}, but more than 10 μmol · l^{-1} is needed to prevent the amastigote form from entering vertebrate cells [3, 4].

The mechanism of action of nifurtimox is still not completely understood. Its trypanocidal action may be related to its ability to form chemically reactive radicals that cause the production of toxic, partially reduced products of oxygen [5]. The dose required to maintain a therapeutic effect ranges from 5 to 20 mg · kg^{-1} body weight. The usual dose is 15 mg · kg^{-1}.

Adverse effects occur in 40 to 70% of patients. The central nervous system is mostly affected, the principal symptoms being irritability, convulsions, and sleeplessness. Gastrointestinal disturbances (mostly nausea) occur frequently. The symptoms are dose related [6, 7].

In 1980, a patient with chronic renal failure who had undergone renal transplantation, died as a result of an infection with *Trypanosoma cruzi*, at the Nephrology Centre of the Clinical Hospital of the Universidad de Chile. Thambo et al. [8] showed that about 11% of patients undergoing haemodialysis and who needed renal transplantation were infected with *Trypanosoma cruzi*. For this reason all patients with a positive serum test for *Trypanosoma cruzi* who admitted to the Nephrology Centre are treated with nifurtimox before renal transplanatation. The current drug regimen has been developed through trial and error, and there is no pharmacokinetic information about nifurtimox in healthy subjects or in patients with renal or hepatic disease.

The disposition of nifurtimox in patients with chronic renal failure has now been investigated.

Subjects and methods

Patients

7 patients with chronic renal failure were studied (5 f and 2 m, 24–60 y, 42–74 kg). All had a creatinine clearance below 10 ml · min^{-1} and were undergoing regular haemodialysis. All had a negative serological test for Chagas' disease. Their details are listed in Table 1. The only exclusion criteria were pregnancy and severe cardiovascular instability. The kinetics of nifurtimox were studied on a non-dialysis day.

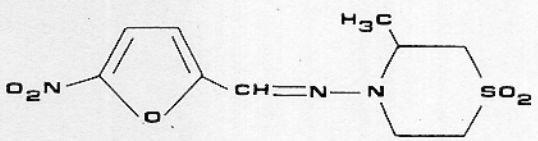

Fig. 1. Structure of nifurtimox

Table 1. Clinical characteristics of the patients with renal failure undergoing haemodialysis

Patient	Sex	Age (y)	Weight (kg)	Serum creatinine ($\mu mol \cdot l^{-1}$)	Creatinine clearance ($ml \cdot min^{-1}$)	Blood urea nitrogen ($mmol \cdot l^{-1}$)	Haematocrit (%)	Total bilirubin ($\mu mol \cdot l^{-1}$)	AlT (I.U)	AST (I.U.)	Alkaline phosphatase (I.U.)
E.V	F	42	53	1000	7.6	12.8	28	11.2	16	8	96.0
S.P	F	60	43	855	7.2	5.8	24	10.0	12	10	85.0
R.S	F	27	42	555	10.7	8.9	34	6.9	15	6	83.0
L.M	M	47	61	682	10.4	6.3	20	4.0	10	9	78.0
L.R	F	24	52	927	9.7	6.2	20	5.2	7	8	73.0
S.Z	M	32	74	1546	6.4	9.5	18	6.9	8	9	75.0
S.C	M	37	56	827	10.3	12.6	23	13.8	20	10	108.0
Mean		38.4	54.6	913	8.9	8.9	24	8.3	12.6	8.6	85.4
(SD)		(12.5)	(10.9)	(293)	(1.6)	(2.8)	(5)	(3.3)	(4.3)	(1.3)	(11.6)

AlT = Alanine aminotransferase
AST = Aspartate aminotransferase

Table 2. Pharmacokinetics (mean, SD) of nifurtimox in 7 patients with renal failure and 7 healthy volunteers

	Patients	Healthy controls	*P*
k_a (h^{-1})	0.973 (0.538)	0.767 (0.204)	NS
λ_z (h^{-1})	0.209 (0.061)	0.260 (0.077)	NS
$t_{1/2_a}$ (h)	0.92 (0.50)	0.95 (0.24)	NS
$t_{1/2_z}$ (h)	3.53 (0.84)	2.95 (1.19)	NS
AUC ($ng \cdot ml^{-1} \cdot h$)	9,510 (3,120)	5,430 (2,190)	< 0.05
V_z/f (l)	529 (428)	755 (283)	NS
CL/f ($l \cdot h^{-1}$)	99.7 (60.3)	193.4 (93.2)	< 0.05
C_{max} ($ng \cdot ml^{-1}$)	1,290 (620)	751 (246)	< 0.05
t_{max} (h)	2.35 (0.93)	2.24 (0.53)	NS

A group of seven healthy subjects was also studied (5 m and 2 f; 23–31 y; 55–60 kg). The results in them have recently been reported elsewhere [9].

On the study day the subjects fasted and took no medication other than nifurtimox. The patients with chronic renal failure stopped taking other drugs 48 h before hand.

Written informed consent was obtained from each participant according to the protocol, which was approved by the Institutional Boards of the Clinical Hospital, Universidad de Chile.

Study protocol

The subjects took a single oral dose of nifurtimox 15 $mg \cdot kg^{-1}$ in rounded off to the nearest number of 120 mg tablets (Lampit®, Bayer Laboratories, Buenos Aires, Argentina).

After administration blood samples were obtained from the forearm at: 0, 1, 2, 3, 3.5, 4, 5, 6, 7, 8.5, and 10 h for the patients, and 0, 0.5, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, and 11 h for the healthy subjects.

Blood was collected in plastic disposable syringes and centrifuged to separate the serum, which was frozen for 24 h until assayed.

Assay of nifurtimox

The serum samples were analyzed by HPLC as previously reported [10]. The method is specific for unchanged nifurtimox and has a limit of sensitivity of 40 $ng \cdot ml^{-1}$.

Data analysis

A one-compartment open model was used in the analysis. The absorption rate constant (ka) was calculated by the method of residuals. The elimination rate constant (λ_z) was determined from the slope of the terminal linear segment of the semilogarithmic plot of serum concentration versus time by the method of least-squares best fit. The area under the serum concentration versus time curve was calculated by the linear trapezoidal method for the first 10 or 11 h extended to infinity by integration.

Since there is no parenteral form of nifurtimox, and its systemic availability is unknown, it was not possible to calculate the distribution volume and total clearance. Instead, the apparent distribution volume (V/f) and an apparent oral clearance (CL/f) by conventional methods.

t_{max} was obtained from the following equation:

$$t_{max} = \frac{\ln (k_a - \lambda_z)}{k_a - \lambda_z}$$

Differences in pharmacokinetics between the groups were analyzed by two-tailed unpaired Student's t-tests with $P < 0.05$ as the minimum level of significance. The power of the study was determined by the method of Stolley et al. [11]. A 30% difference in mean values for CL/f was chosen as the smallest difference of potential clinical significance between patients and controls, and a sample size of seven in each group was calculated to be the minimum required to detect this difference with alpha = 0.05 and beta = 0.20.

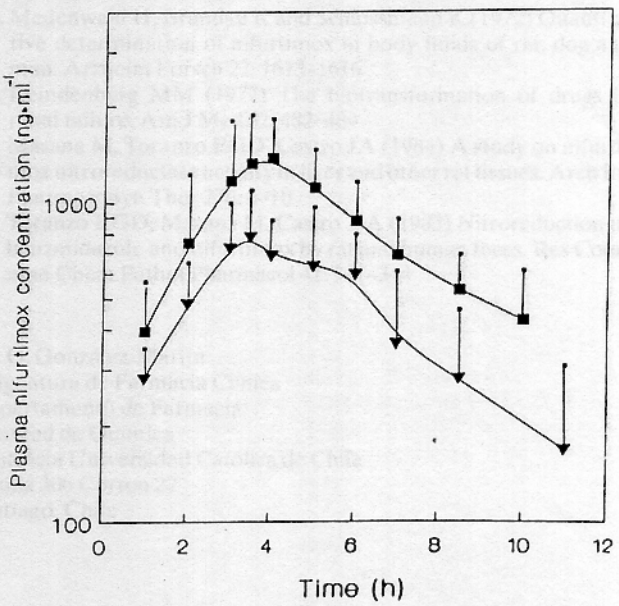

Fig. 2. Serum nifurtimox concentrations (mean ± SD) after 15 $mg \cdot kg^{-1}$ PO in patients with severe renal impairment (■) and in healthy subjects (▼)

Results

The pharmacokinetics of nifurtimox in seven healthy volunteers and the seven patients after an oral dose of 15 $mg \cdot kg^{-1}$ is summarised in Table 2. The mean serum concentration-time profiles for both groups are shown in Fig. 2.

There was a significant increase in C_{max}, AUC, and oral clearance in the patients with renal failure compared to the healthy subjects. Although the mean half-life of nifurtimox was prolonged in the patients, the difference was not statistically significant.

Discussion

The disposition of nifurtimox in chronic renal failure was altered compared with healthy subjects.

Oral absorption of nifurtimox was rapid, but the peak serum concentration was significantly higher in renal failure. Since there is no parenteral dosage form of nifurtimox, its absolute systemic availability is not known. However, it is suspected that it undergoes extensive first-pass hepatic metabolism. Duhm et al [12] showed that radioactive nifurtimox was well absorbed from the gastrointestinal tract in rats. However, nifurtimox is extensively metabolized in animals, and Mendewal [13] reported that only 0.5% of a single oral dose of nifurtimox was recovered as unchanged drug in the urine in rats and dogs. These findings suggest that nifurtimox undergoes extensive first-pass metabolism in the liver.

The patients with chronic renal failure had a larger area under the curve than the healthy volunteers. This could be explained by an increase in systemic availability or a reduction in clearance. There was a significant difference in the apparent clearance between the groups, the patients with renal failure having a 50% lower clearance. Because a large fraction of nifurtimox is metabolized in the liver, this difference could be accounted for by a reduction in metabolic clearance, since some liver enzyme reactions are reduced in chronic renal disease, especially those involving reduction [14]. Previous studies [15, 16] have suggested that cytochrome P-450 and P-450 reductase are involved in the nitroreduction of nifurtimox.

On the other hand, the patients had a higher C_{max} than the healthy volunteers. This could have been due either to an increase in the systemic availability of the drug or to a decrease in the distribution volume, since renal failure may alter the distribution volume of drugs [14].

The simplest explanation is that the change in C_{max} was due to a change in the systemic availability and this can be explained in terms of inhibition of first-pass metabolism. The disproportionate changes in CL/f and V/f would have been due to the difference in λ_z, which turned out to be non-significant.

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