Study of the Serum Half-Life of a New Cephalosporin in Uraemic Patients

J P FILLASTRE, G HUMBERT, J ACAR, H MALANDAIN, M ROBERT, D DUBOIS, M F DAUFRESNE
Hôpital Charles-Nicolle, Rouen, France

The sodium salt of 7 - cyanoacetyl-amino-cephalosporanic acid is a new semisynthetic cephalosporin (CIBA 36, 278 ba). This new antibiotic is excreted in high concentration in the urine. It has a broad antibacterial spectrum and is bactericidal for both gram positive and gram negative organisms (Knusel, 1970). It can be administered intramuscularly or intravenously. Possible accumulation in the uraemic patient had yet to be studied.

PATIENTS AND METHODS

Six healthy subjects, aged between 25 and 34, were each given 1 g of the new cephalosporin by intramuscular injection. Blood samples were taken 30 min, 1 hour, 2, 3 and 4 hours after the injection. The urine was collected after 6 hours. The cephalosporin was also given intravenously (1 g) to 4 of these controls. Blood samples were taken after 15 and 30 minutes, 1 hour, 2, 3 and 4 hours.

Forty-two uraemic patients aged between 18 and 72 were divided into 4 groups:

GROUP I: 16 patients with creatinine clearance (C_{CR}) of 20-80 ml/min.
GROUP II: 7 patients with C_{CR} of 5-20 ml/min.
GROUP III: 7 patients with C_{CR} less than 5 ml/min.
GROUP IV: 12 patients on haemodialysis. C_{CR} : 0-2 ml/min.

1 g of cephalosporin im was given to the patients of the first 3 groups; blood samples were taken at 0, 1, 2, 4, 6, 12, 24 and 48 hours after injection.

The patients on haemodialysis were studied between dialysis sessions and during dialysis. There was a week between the two studies. In both cases 1 g cephalosporin was given intravenously. Blood samples were taken at 0, 1, 2, 4, 6 and 12 hours in the inter-dialysis studies. Blood samples,
from both before and after the coil, were taken at 0, 1, 2, 4, 6 and 8 hours during dialysis. Coil dialysers (Ultraflo 145) were used with a blood flow rate of 1000 ml/min.

Creatinine clearance was measured using the Auto Analyser modification of Jaffé's method. The cephalosporin CIBA 36.278 ba was assayed by agar plate diffusion using bacillus subtilis ATCC 66.33 (5 x 10^6 spores/ml) as the test organism. Pooled normal human serum was used for the control; a standard curve was obtained. The patients' sera were diluted with phosphate buffer solution (pH 6.6). Incubation at 37°C was carried out for 18 hours. The inhibition zones were read using a Zeiss enlarger. The serum concentrations of cephalosporin were plotted on a semilogarithmic scale against time to find the half-life.

RESULTS

Serum half-life of the new cephalosporin after intramuscular administration

In the controls the concentration peak was at 30 minutes (17.1 µg/ml). The serum half-life (T 1/2) was 1 hour 02 minutes. 50-100% of the injected dose had been excreted in 6 hours.

In the uraemic patients the concentration peak was obtained after 1 or 2 hours; the serum T 1/2 was prolonged.

Group I: The average peak serum concentration was 31.53 ± 5.03 µg/ml. After 6 and 12 hours the average serum concentrations were 7.94 ± 1.70 µg/ml and 2.64 ± 0.78 µg/ml respectively. The serum T 1/2 was 3 hours 06 minutes ± 0.28 min. 75% of the injected dose had been excreted in 24 hours.

Group II: The average peak serum concentration was 59.14 ± 4.78 µg/ml. After 12 and 24 hours, the average serum concentrations were 19.81 ± 3.14 µg/ml and 10.23 ± 1.72 µg/ml respectively. The serum T 1/2 was 11 hours 0.3 min ± 1 hour 39 minutes.

Group III: The average peak serum concentration was 64.43 ± 8.09 µg/ml. After 12, 24 and 48 hours the average serum concentrations were 26.11 ± 4.36 µg/ml, 18.43 ± 2.23 µg/ml and 7.86 ± 1.40 µg/ml respectively. The serum T 1/2 was 16 hours 55 minutes ± 1 hour 24 minutes.

Serum half-life of the cephalosporin after intravenous administration

In the controls serum T 1/2 was 38 minutes whereas it was 4 hours 30 minutes in the dialysis patients, in the interdialysis studies. During dialysis the T 1/2 was only 2 hours 36 minutes; the extraction percentage was 27 to 33%.
DISCUSSION

In uraemic patients the serum half-life of this new cephalosporin is increased so it is necessary to adapt dosage to renal function.

In normal subjects 1 g cephalosporin im every 6 hours or 2 g ip every 8 hours should be given. This dosage can be used in patients with a $C_{cr}$ of 20-80 ml/min. In patients with $C_{cr}$ 5-20 ml/min, 1 g of cephalosporin im should be given every 24 hours. In patients with $C_{cr}$ of less than 5 ml/min, 1 g of cephalosporin im should be given every 48 or 72 hours. In haemodialysis patients 1 g of cephalosporin should be given iv at the end of dialysis and repeated every 12 hours.

SUMMARY

A new cephalosporin (the sodium salt of 7-cyanoacetyl-amino-cephalosporanic acid) excreted mainly in the urine was given parenterally to healthy subjects and uraemic patients. The dose of this antibiotic should be adapted according to renal function. As long as the $C_{cr}$ remains above 20 ml/min the same dose may be injected as to a normal subject. When the $C_{cr}$ is reduced to 5-20 ml/min, 1 g cephalosporin im every 24 hours is adequate. In anuric or maintenance haemodialysis patients 1 g iv should be given every 12 hours.
ACKNOWLEDGMENT

We thank Ciba Laboratories for supplying the cephalosporin.

REFERENCE