Pharmacokinetic Studies of Cefuroxime and Dosage Recommendations in Patients with Impaired Renal Function

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Potent antibiotics such as cefuroxime are not only given to patients with normal kidney function. On the contrary, patients who need a highly active broad spectrum antibiotic are often in a poor clinical condition with circulatory impairment and consequent reduced renal plasma flow and glomerular filtration rate (GFR). It is necessary to know the correct dosage for these severely ill patients and other patients with renal failure, because no antibiotic is entirely without toxic limitations. There is some evidence that cephalosporins can cause tubular damage, first described by Perkins *et al.* (1968) and cerebral toxicity e.g. stupor and convulsions (Heinecke *et al.* 1976). It was therefore decided to clarify the extent to which the serum half life time (HLT) of cefuroxime is influenced by renal impairment.

Materials and Methods

Twelve male and 9 female adults with a mean age of 47 ± 11 years, a mean height 168 ± 8 cm, a mean body weight of 66 ± 11 kg, and a mean body surface area of 1.77 m^2 were involved in this study. Patients received cefuroxime i.v. as single injections. All were given 750 mg of cefuroxime except 4 patients who received 1.5 g. The originally intended dosage regimen of 1.5 g of cefuroxime was modified to 750 mg because the serum levels of 1.5 g were relatively high and inconvenient to determine. This simplification of the method seemed to be acceptable because the half life time of cephalosporins and penicillins is not influenced by the quantity administered, within this range of dosage. Single injections of 750 mg are also recommended by the manufacturer.

Plasma samples were obtained before the injection and 30, 60, 90, 120, 150 and 240 min afterwards. In special cases the times of plasma determinations were changed, especially in patients with severe renal failure where the follow up was prolonged. The cefuroxime concentration was assayed using the standard cup plate method (Bauer *et al.* 1956, Höffler 1971; test strain *Staphylococcus aureus* C 864). The GFR was determined by ^{51}Cr-EDTA by the single shot method. Computer calculations were done by Hewlett-Packard 65.

Results

The apparent volume of distribution was determined as $21.3 \pm 5.51\%$ of the body weight. The distribution volume of ^{51}Cr-EDTA was found to be $21.2 \pm 3.73\%$ of the body weight. These figures are nearly identical.

The relation between GFR and HLT is best expressed by the power function

(1) $HLT = 780 \times GFR^{-0.565}$ ($r = 0.9294$; see also Fig 1).

In a very simplified form, the HLT could be calculated from the equation

(2) $HLT = 700/\sqrt{GFR}$

Discussion

The findings reported here are not unexpected. The distribution volume of all previously examined cephalosporins (cephaloridine, cephalothin, cephradine and cefamandole) and penicillins (ampicillin, carbenicillin, dicloxacillin, flucloxacillin and ticarcillin) were found to be of the same order, i.e. approximately 20% of the body weight. This is the range of the extracellular space. Indeed no antibiotic could be found in centrifuged and disrupted red blood cells, except for a small amount which corresponds to the 'trapped plasma'. It was also to be expected that the correlation between GFR and HLT would best be expressed by a power function. The same correlation could also of course be found with other substances mentioned above.

The data underline the requirement for dosage reduction in cases of renal failure. For this purpose we recommend the so-called isoconcentration dosages (ICD). By using these it is intended to achieve concentrations equal to those obtained by normal dosage in normal renal function. Such ICDs are shown in Table 1. A precise definition was developed for the case of cephradine pharmacokinetics by Höffler & Koeppe (1975), and a brief definition follows.

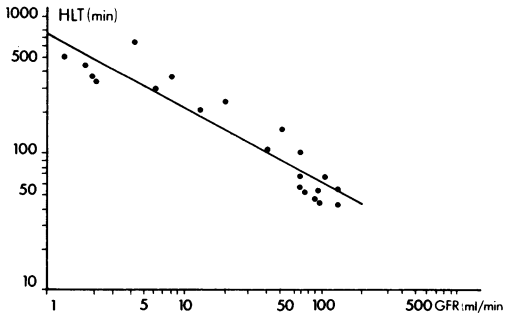

Fig 1 *The correlation between GFR and HLT of cefuroxime expressed as a power function. In spite of the high correlation coefficient ($r = 0.9294$) the interindividual differences are considerable. Consequently only a rough estimate of HLT by means of GFR or plasma creatinine is possible*

Table 1

Isoconcentration dosages

GFR (*ml/min/ 1.73 m²*)	*CR* (*mg %*)	*HLT* (*min*)	*DOS* (*g*)	*DI* (*h*)	%
110	0.8	55	0.75	8	100
45	2.0	91	0.75	8	100
18	3.5	152	0.75	12	66
8	6.0	241	0.375	8	50
2	15.5	527	0.375	24	16.6
0.5	—	1153	0.1875	24	8.3
110	0.8	55	1	8	100
45	2.0	91	1	8	100
18	3.5	152	1	12	66
8	6.0	241	0.75	12	50
2	15.5	527	0.5	24	16.6
0.5	—	1153	0.25	24	8.3
110	0.8	55	1.5	8	100
45	2.0	91	1.5	8	100
18	3.5	152	1.5	12	66
8	6.0	241	0.75	8	50
2	15.5	527	0.75	24	16.5
0.5	—	1153	0.5	24	11.11
110	0.8	55	3	8	100
45	2.0	91	3	8	100
18	3.5	152	2	8	66
8	6.0	241	1.5	12	33
2	15.5	527	1	12	22
0.5	—	1153	1	24	11

GFR = glomerular filtration rate; CR = plasma creatinine; HLT = mean value of expected half life time; DOS = dosage; DI = dosage interval; % = % of the recommended normal dosage in normal renal function

Use of the table:
(1) Assign the individual case by clinical and biochemical data to 1 of the 6 grades of renal function
(2) Read the dosage and the respective dosage interval. In extremely impaired renal function 1/2 or 1/4 vial should be used

On the basis of the experimentally evaluated distribution volumes and the HLT, derived from GFR or plasma creatinine (equation 1), estimations can be made of the plasma levels which can be expected on different dosage regimens. The mathematical model for such estimations was given by Dost (1968) and Koeppe & Höffler (1972, 1976) have established computer programmes for this formula. By using these estimations we recommend isoconcentration dosages (ICD) which have to fulfil two requirements:

(1) As described in several studies, the toxicity of an antibiotic is dependent on maximum concentrations. For this reason the ICD should not lead to a higher maximum concentration (C max) than that which can be expected in normal renal function and normal dosage regimens.
(2) Since however the C max is not *per se* responsible for toxic effects but the mean concentration might also exert an influence, a second requirement should be fulfilled. C should not exceed twice the value achieved at normal renal function and normal dosage regimens. C is the concentration that would result if all the doses were given continuously, e.g. as i.v. drips. It would have been possible, of course, to choose as the second condition, not $C \times 2$, but $C \times 1$. In this case one would give up the greater therapeutic safety (which is achieved by increased concentration) resulting from the prolonged HLT in impaired renal function. This would be the case, for example, when using the following formula:

$$(3)\ \frac{\text{normal HLT}}{\text{prolonged HLT}} = \frac{\text{normal dosage interval}}{\text{X (interval in question)}}$$

Thus

$$(4)\ X = \frac{\text{normal dosage interval} \times \text{prolonged HLT}}{\text{normal HLT}}$$

Our definition of ICD, written in a mathematical form is as follow:

(5) C max in normal renal function $\geqslant$ C max when using ICDs,

(6) $C \times 2$ in normal renal function $\geqslant$ C when using ICDs

In the special clinical situation of i.v. drip infusion the definition is

(7) C in normal renal function = C using ICDs

It has to be emphasized that there is a great interindividual deviation of HLT (Fig 1), so that only the dimensions of the values in Table 1 are valid.

Although cefuroxime is known as a substance with good therapeutic tolerance at normal dosages, toxic reactions can be expected in patients with renal insufficiency, because up to 10-fold prolongations of the HLT may occur. For this reason we feel obliged to stress that the essential dosage reduction, which has been evaluated here, is to be brought to the attention of the attending doctor to prevent the misuse of a very useful substance.

Summary

The extent to which the serum half life time of cefuroxime is affected by renal impairment was studied in 12 male and 9 female patients who were given a single i.v. injection of 750 mg. Plasma samples were obtained before the injection and 30, 60, 90, 120, 150 and 240 min after injection. The plasma concentrations were determined by the cup plate method using *Staphylococcus aureus*. On the basis of these values, the half life time and the distribution volume were calculated by computer programme.

The distribution volume of cefuroxime was found to be 21.3 ± 5.51 % of the body weight. The

relation between half life time and glomerular filtration rate (GFR) is best expressed by a power function. The data indicate the need for a dosage reduction in renal impairment, if GFR is below 18 ml/min. For this purpose so-called 'iso-concentration dosages' (ICD) are recommended, which lead to nearly identical (and not higher) maximum plasma concentrations in patients with various degrees of renal function. Such ICDs are tabulated. When used, cefuroxime even in extreme situations (e.g. the bilateral nephrectomized patient) is a safe antibiotic from the toxicological point of view.

Acknowledgments

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REFERENCES

Bauer K, Hiltmann R, Schmid J & Auhagen E (1956) *Medizin und Chemie*, Vol. 5

Dost F H (1968) Grundlagen der Pharmakokinetik, Stuttgart

Heinecke G, Höffler U & Finke K (1976) *Clinical Nephrology* **5**, 45

Höffler D (1971) Antibakterielle Therapie bei Niereninsuffizienz Beecham Pharma, Mainz

Höffler D & Koeppe P (1975) *München medizinische Wochenschrift* **117**, 1169

Höffler D, Koeppe P, Fuchs E & Fiegel P (1972) *International Journal of Clinical Pharmacology* **5**, 450

Koeppe P & Höffler D (1972) *Arzneimittel Forschung* **22**, 331 (1976) Pharmakokinetische Grundrechnungen mit einem Taschenrechner in Pyelonephritis (Kienatz ed), p 299, Editiones Roche

Perkins R L, Apicalla M A, Lee J S, Cuppage F E & Saslaw S (1968) *Journal of Laboratory and Clinical Medicine* **71**, 75

DISCUSSION

Dr R Norrby (*Gothenburg*) was sceptical about the use of a fixed dosage in patients with markedly impaired renal function. As Professor Höffler had pointed out, there was a logarithmic relationship between the half life and the creatinine clearance. However, in his experience creatinine clearance was not a particularly good test. Enormous variations occurred in the same patient from day to day and he thought it more appropriate to monitor the dose of cefuroxime by following serum concentrations in these patients. It was done for gentamicin and was not enormously difficult. There was a high risk of over-treating or under-treating patients with markedly impaired renal function if a nomogram was used.

Dr Sack said that the data were being obtained but so far they were not available.

Professor Neu (*Chairman*) asked Dr Kosmidis how he defined 'cure'. It was not clear if a cure was defined at the end of 2 weeks or of 6.

Dr R Rangoonwala (*Frankfurt*) asked Dr Kosmidis to identify the indole-positive *Proteus* species he had been treating.

Dr Kosmidis said for urinary tract infections cure was defined at 2 weeks. Some individuals (though not all) were followed-up at 6 weeks.

For other infections, cure was defined as complete clinical cure plus eradication of the organism. In cases described as 'improvement' there was complete clinical cure although the organism was still in the chest. He had described the only case of failure.

The organisms involved were as follows: 1 case of *Proteus rettgeri*, recurrent pyelonephritis in a 72-year-old female. It was cured and the organism was eradicated after 10 days of treatment, 3 g of cefuroxime daily. Creatinine clearance was 68. One case of *Proteus vulgaris* acute pyelonephritis in a man of 63, cured with eradication by 3 g of cefuroxime daily. Creatine clearance was 54. One case of *Proteus rettgeri* pyelonephritis in a 71-year-old man which was cured and the organism eradicated. Creatinine clearance was 42. One mixed infection with *Proteus vulgaris* plus *Enterobacter ærogenes* causing septicæmia and pelvic abscesses. The patient had over a long period been treated with amikacin and other antibiotics. He was anuric and was receiving peritoneal dialysis. He was cured and the organism eradicated. In one case of *Proteus vulgaris* chronic pyelonephritis, the patient improved and the organism was eradicated, as was the same organism in another patient with recurrent pyelonephritis on hæmodialysis.

In answer to the Chairman's question, he said that even though some patients had received nephrotoxic antibiotics before, in no case was there any deterioration of renal function. Following therapy, some of them had shown improved creatinine clearance.

Dr D M Ryan (*Greenford*) said that in Dr Sack's experimental pyelonephritis system he had found that cefazolin and cefuroxime were comparable and were both more active than other parenterally available cephalosporins. They had taken this work a stage further and compared cefazolin and cefuroxime against Gram negative bacilli producing lactamase. In these experiments, the therapeutic results could be related to the MIC of the organism and again cefuroxime was superior to cefazolin.

Dr E Rubinstein (*Tel Hashomer*) drew attention to the considerable differences in half-life time, particularly with creatinine clearance rate of 50–100. He wondered what could account for the differences between Professor Höffler's and Dr Kosmidis's results.

Dr Kosmidis confirmed that he, like Professor Höffler, had used a 2-compartment open model. They took the lowest part of the line, which was about twice as high as their lowest sensitivity limit. In some cases, however, the drug had probably entered a third phase, making the half-life longer.

Professor W Brumfitt (*London*) asked whether a creatinine clearance level of 50 was sufficiently severe to require monitoring in what was believed to be a relatively safe drug. In some patients, creatinine clearance had been below 20. He asked Professor Höffler whether he regarded it as necessary simultaneously to estimate the cefuroxime levels to validate his calculations.

Professor Höffler had done so on a random basis and had obtained good correlation between calculated and measured levels. He believed that dose reduction was necessary only at glomerular filtration rates below 20–30 ml. It had to be stressed that there were very great inter-individual differences. It was necessary to measure the blood levels continuously to overcome this problem. Such a procedure was possible only in a very few centres.

Professor Neu (*Chairman*) said that in most institutions it was not possible to measure clearances below 30 very accurately. In all the studies so far presented the drug showed reproducibility of blood levels whether patients were uræmic or non-uræmic. It was also non-toxic and he wondered whether it was necessary, once these data had been validated, to perform these blood level and other studies, except perhaps in the rare case of *Proteus rettgeri*. They were perhaps drawing an analogy with very toxic drugs like the aminoglycosides which was inappropriate for this very safe compound.

Dr Kosmidis and Professor Höffler agreed. The latter added that he had seen patients receiving other cephalosporins suffer from coma and Jackson type seizures and die, only because they received normal doses when in impaired renal function. It was a mistake to expect the tables such as those he had presented, to give exact predictions. They must be particularly on guard to avoid therapeutic failures.

Professor G S M Kellaway (*Auckland*) congratulated Dr Kosmidis on his presentation. Creatinine clearance was certainly difficult to determine at rates less than 15 ml/min, particularly in patients with changing renal function in acute illness. He asked whether Dr Kosmidis had found it necessary to determine creatinine clearance rate, or whether correlation with serum creatinine was sufficiently good to rely on this latter measurement only.

Dr Kosmidis said that they had used creatinine clearance. It was not ideal but it was probably satisfactory for this drug.

Professor Daikos said that such patients were commonly found in renal units and serious infection caused them considerable problems. If they were treated with aminoglycosides then clearly they should be monitored. But with β-lactam antibiotics the situation might not be so critical. Of the cephalosporins, cefuroxime was found the most effective, and even with very low renal function it produced levels sufficient to treat some of the most difficult cases, those of indole-positive *Proteus*.

Professor Neu (*Chairman*) asked Dr Kosmidis what percentage of urine recovery he had in patients with creatinine clearance levels of less than 10 ml/min.

Dr Kosmidis said that of the 6 cases with creatinine clearance levels below 10, there were 5 cures and 1 improvement. He had measured urine levels in most of the patients. They were in the range of 30–100 μg/ml in those patients who had urine. Urinary levels were not measured in 1 patient with hæmodialysis. He produced urine but was not included in the kinetic study. But other patient volunteers were included in the kinetic study during hæmodialysis.