Carbenicillin Half-Life Time in Patients with Acute and Chronic Renal Failure. Effects of Haemodialysis

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The merits of carbenicillin as an antibiotic active against Pseudomonas, E. Coli and Proteus species are well established (Acred et al, 1967; Brumfitt et al, 1967).

Its specific antibacterial spectrum makes it particularly useful in urinary infections (Bodey et al, 1969; Brumfitt et al, 1967; Malmborg, 1967). Since carbenicillin is eliminated through the kidneys, and considering that kidney function is often depressed in patients with urinary infections, it is most important to determine the influence of different degrees of kidney insufficiency on the excretion of the drug.

So far, there are few available investigations on this problem (Bodey et al, 1969; Brumfitt et al, 1967; Eastwood & Curtis, 1968). They cover a rather small number of cases, and because of this, the information they give is not exhaustive.

As regards haemodialysis in particular the only data published refer to three patients (Eastwood & Curtis, 1968).

MATERIAL AND METHODS

Number of cases

Eighteen patients with chronic renal failure (CRF) (mean GFR = 53 ml/min) were studied. In addition 14 determinations were made in 8 acute renal failure (ARF) cases: 8 before and 6 after haemodialysis.

Control cases: 7

Technique: 1 g of carbenicillin* was injected i.m. Blood samples were taken before the injection and 30, 90, 210 and 450 minutes after. In the haemodialysis cases (Kollf twin coil kidney) the injection was made just before starting the dialysis.

*The carbenicillin (Pyopen) used in this study was kindly supplied by Beecham Research Laboratories

Carbenicillin levels were measured by means of a serial tube dilution method using a Staphylococcus aureus whose sensitivity (minimal inhibitory concentration (MIC) to carbenicillin was 0.37 μg/ml.

The data obtained were plotted on semilogarithmic paper against time. The resulting curve gave the half-life time (T 1/2) of the drug.

RESULTS

In the control cases the calculated T 1/2 of carbenicillin (Figure 1) was 1 hour 8 minutes (52-94 minutes). In the CRF cases (Figure 2) it was 3 hours and 24 minutes (88-310 minutes). It should be noted that in the individual cases there were very different values, which were nevertheless in proportion to the renal functional impairment.

In the ARF cases (Figure 3) the mean T 1/2 of carbenicillin before haemodialysis was 13 hours and 52 minutes. It is worth mentioning that the range was very large, i.e. 10 hours 22 to 23 hours 11 minutes, in spite of the fact that this group was very homogeneous (renal function nil) after haemodialysis (Figure 3) the mean T 1/2 was shortened to 5 hours 35 (4 hours 10 minutes - 6 hours 45 minutes).

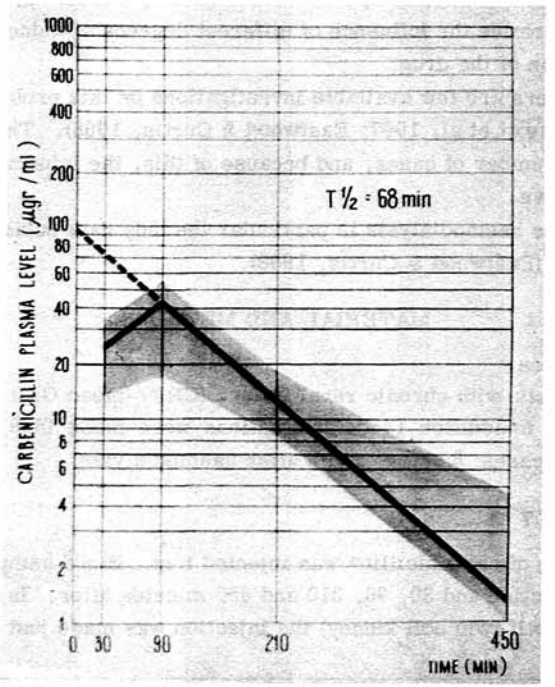

Figure 1. Graph of mean carbenicillin plasma levels, after 1 g i.m. carbenicillin in control cases. Solid line before haemodialysis and dotted line after haemodialysis

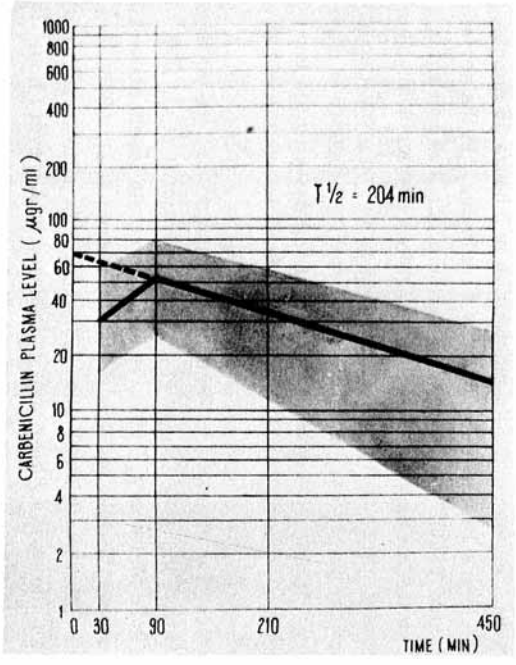

Figure 2. Graph of mean carbenicillin plasma levels, after 1 g i.m. carbenicillin in patients with chronic kidney failure. Solid line before haemodialysis and dotted line after haemodialysis

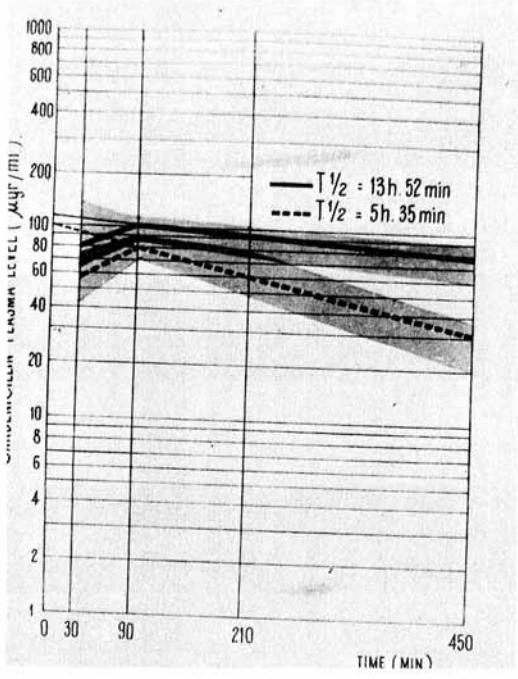

Figure 3. Graph of mean carbenicillin plasma levels, after 1 g i.m. carbenicillin in patients with acute renal failure. Solid line before haemodialysis and dotted line after haemodialysis

DISCUSSION

The determination of the correlation between the evolution of carbenicillin plasma levels and the extent of renal dysfunction is of utmost importance in adjusting the therapeutic level of the drug in a particular infection, whilst avoiding at the same time possible toxic concentrations.

To our knowledge there are only two other papers on this subject: one by Bodey et al (1969), who found in five patients with a GFR of 60-85 ml/min carbenicillin plasma concentrations which implied a mean T 1/2 of about 140 minutes and the second by Eastwood and Curtis (1968), who found in patients with a GFR less than 5 ml/min a mean T 1/2 of 12.5 hours. On considering these three investigations, which extend over a large range of GFR, we can conclude that there exists a proportional relation between the amount of the GFR reduction and the prolongation of the T 1/2 of the drug.

It seems, therefore, that the determination of the GFR alone can give enough information on the dose and rate of administration of carbenicillin that will ensure the correct plasma levels in a given case. However, because of the large differences between the individual cases it is advisable to check the actual concentrations achieved at least once.

The same comment can be made on the carbenicillin half-life time in ARF cases. In spite of the homogeneous character of the renal dysfunction (anuria) the T 1/2 in our series varied between 10 hours 22 minutes and 23 hours 11 minutes, whereas in the cases described by Eastwood and Curtis (1968) the only anuric patient in which it was determined showed a T 1/2 of 8.3 hours. The reduction in the T 1/2 brought about by the haemodialysis is also unequal. In our series its mean value is 5 hours 35 minutes, the range being 4 hours 10 minutes - 6 hours 45 minutes. In the series of Eastwood and Curtis (1968), who worked on patients who still had some urine output, the mean value was 4.5 hours, the range being 4.2 - 4.7 hours.

Fortunately, these individual differences are of no great importance from a practical standpoint, because of the very low toxicity of carbenicillin. Thus, the only significant error would be in administering too low a dose. On the other hand, the high price of the drug must be considered to avoid wasteful use.

In practice, for example in Pseudomonas infections, the principal clinical application of the drug (Bodey et al, 1969; Brumfitt et al, 1967; Jones & Lowbury, 1967; Malmborg, 1967), in order to obtain levels above 100 μg/ml, which represents the MIC for this organism (Acred et al, 1967; Brumfitt et al, 1967) the following schedule should be used. In patients with normal renal function the starting dose is 2 g, followed by 1 g every hour (the normal T 1/2 of the drug). In renal cases, regardless of the value of the GFR, the starting dose is the same as above. The subsequent 1 g dose is to be administered every 2 hours when GFR is 65-80 ml/min, every 3-4 hours,

when GFR is 40-65 ml/min, probably every 6-8 hours when GFR is 10-40 ml/min and every 8-12 hours, when GFR is less than 5 ml/min. In ARF cases the 1 g dose should be administered every 12 hours, but during haemodialysis the interval should be 4-5 hours.

The only exception to this schedule seems to be urinary tract infection, as eradication of infection has been obtained with only 4 g/day in patients with normal kidney function (Brumfitt et al, 1967; Malmborg, 1967; Stratford, 1968). This can be explained on the grounds that in this kind of infection the urinary concentration is more important than that in plasma. This assumption is supported by one anuric case in whom pseudomonas cystitis persisted in spite of the fact that the carbenicillin plasma levels reached 750 μg/ml (Darrell & Waterworth, 1969).

If this proves to be correct, then urinary infection is the only type requiring an increase in carbenicillin dose as the renal function is failing.

Of course, in E. Coli and Proteus spp. infections the schedule should be adapted according to the MIC of carbenicillin against the specific organism.

SUMMARY

Carbenicillin half-life time has been studied in patients with chronic renal failure, acute renal failure and during haemodialysis. An administration schedule, corresponding to different degrees of renal functional impairment, is suggested. In general, the dose must be reduced in proportion to the extent of the kidney failure. On the contrary, in urinary infections it must be increased as kidney function fails.

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