Carbenicillin Administration in Patients with Severe Renal Failure

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Knudsen, Rolinson, and Sutherland (1967), Jones and Lowbury (1967), and Brumfitt, Percival, and Leigh (1967) have demonstrated that the majority of *Pseudomonas aeruginosa* strains are inhibited by a carbenicillin concentration of 100 μg./ml. Carbenicillin is very rapidly excreted in the urine under normal circumstances, however, and Knudsen *et al.* (1967) have shown that in patients with normal renal function it would be necessary to administer 1 g. of carbenicillin intravenously every hour together with probenecid in order to maintain serum levels of 100 μg./ml.

The present study was undertaken to determine the dose of carbenicillin necessary to maintain serum levels of about 100 μg./ml. in patients with severe renal failure. As in the previous study (p. 484), informed consent was obtained from all of them. The opportunity was also taken to study the effect of haemodialysis and peritoneal dialysis on serum levels of the drug.

Methods

The concentration of carbenicillin in serum was determined by the cup-plate biological assay method (Knudsen and Rolinson, 1960) with *Ps. pyocyanea* NCTC 10490 (Ellsworth strain ; 1973) as test organism.

Carbenicillin in doses of 1 or 2 g. was given in 20 ml. of 0.9% saline intravenously over five minutes to eight patients with severe renal failure at a time when they were not being dialysed. Venous blood samples were taken at varying intervals after the administration of the drug.

Three of these patients were undergoing twice-weekly haemodialysis and a similar dose of carbenicillin was given to these three patients on another occasion, at the beginning of a dialysis. Arterial blood samples were taken before, during, and at the end of dialysis. Modified two-layer Kiil dialysers were used with cuprophane membrane (PT150). A single pass warm dialysis (37° C.) system was employed and dialysis was carried out for 14 hours at a time.

Two other patients were given another dose of carbenicillin while undergoing peritoneal dialysis. Venous blood samples were taken at varying intervals after the administration of the drug together with aliquots from the peritoneal dialysis fluid. Commercially available peritoneal dialysis solutions were employed (Dialaflex) and 30-minute equilibration periods with 2-litre exchanges were used. Four consecutive exchanges were studied in each patient. All serum and peritoneal dialysate samples were stored at −15° C. until assayed.

Plotting serum concentrations on a semi log. scale against time showed a linear fall in carbenicillin concentration from which the serum half-life was estimated.

Results

The diagnoses and renal function of the patients studied are shown in Table I. The blood urea and creatinine levels are those present when the patients were first seen and before treatment was instituted. The endogenous creatinine clearances in six of the patients were <5 ml./min. with plasma creatinine levels varying from 12.4 to 35 mg./100 ml. One of the remaining patients was anuric and had a plasma creatinine level of 20 mg./100 ml. while the other had an endogenous creatinine clearance of 11 ml./min. and a plasma creatinine level of 10.0 mg./100 ml.

TABLE I.—*Diagnoses and Renal Function in Subjects Studied*

Case No.	Sex	Age	Diagnoses	Blood urea (mg./100 ml.)	P. Cr. (mg./100 ml.)	Cr. Cl. (ml./min.)
1	M	44	Hypertension. Uric acid neph.	168	21·6	4·0
2	F	36	G.N.	280	12·4	3·2
3	M	24	Hypertension, G.N.	216	21·5	2·8
4	F	36	M.H. G.N.	400	20·0	Anuric
5	M	25	M.H. G.N.	420	22·5	3·0
6	M	57	Phenacetin neph.	330	35·0	2·0
7	M	32	Hypertension, G.N.	196	10·0	11·0
8	M	63	Phenacetin neph.	218	16·8	3·0

Urea and creatinine levels are those when patients first presented and before treatment was instituted. P. Cr.=Plasma creatinine. Cr. Cl.=Creatinine clearance. G. N.=Glomerulonephritis. M. H.=Malignant hypertension. Neph.=Nephropathy.

Table II shows the serum levels and half-life of carbenicillin in the eight patients when none of them were undergoing dialysis treatment. The half-life of carbenicillin in these eight patients ranged from 6.7 to 23.5 hours, with a mean of 12.5 (S.D. 6.7).

TABLE II.—*Serum Carbenicillin Levels with* No *Dialysis Treatment*

Case No.	Dose	Serum Carbenicillin (μg./ml.)							Half-life (Hours)
		Zero	1 Hr.	4 Hr.	5 Hr.	8 Hr.	11 Hr.	24 Hours	
1	1 g.	<3·0	95	79	69	54	51	17	9·8
4	1 g.	<3·0	147	125	—	97	—	70	23·0
5	1 g.	<3·0	99	72	—	53	—	9	6·7
8	1 g.	<3·0	100	96	88	66	59	18	8·3
2	2 g.	16·0	247	202	—	161	—	51	10·0
3	2 g.	<3·0	230	190	—	134	—	50	10·5
6	2 g.	<3·0	187	115	—	115	—	73	23·5
7	2 g.	<3·0	190	115	—	98	—	25	8·3

The highest observed levels of carbenicillin in the serum occurred at about one hour after the administration of the drug. In seven patients given 1 g. intravenously the mean serum level at one hour was 103 μg./ml. (range 82–147, S.D. 22). In six patients given 2 g. intravenously the mean serum level at about one hour was 207 μg./ml. (range 183–247, S.D. 26).

Effect of Haemodialysis.—In the three patients undergoing twice-weekly haemodialysis it was possible to give carbenicillin at the beginning of a dialysis and to compare the serum levels and half-life of the drug with those values obtained when the patients were not being dialysed. Table III shows the serum levels and half-life of carbenicillin in the three patients during dialysis. There was a reduction in the half-life of carbenicillin during haemodialysis from a mean of 10.1 hours without dialysis to a mean of 4.5 hours during haemodialysis. This suggests that carbenicillin is dialysed out when the Kiil dialyser is used with cuprophane membrane PT150.

TABLE III.—*Effect of Haemodialysis on Carbenicillin Levels*

Case No.	Dose	Serum Carbenicillin Levels (μg./ml.) During Haemodialysis					Half-life (Hours)
		Pre-dialysis	1 Hr.	4 Hr.	8 Hr.	14 Hours	
1	1 g.	<3·0	86	34	—	9·0	4·5
2	2 g.	<2·0	183	115	49·5	21·0	4·2
3	2 g.	37	205	116	59	28	4·7

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Effect of Peritoneal Dialysis.—In two patients carbenicillin was administered during peritoneal dialysis and the serum levels and half-life were compared with those obtained in these two patients when they were not being peritoneally dialysed. Peritoneal clearances of carbenicillin were obtained in four consecutive exchange periods in each patient. Table IV shows the results of serum levels and half-life obtained during peritoneal dialysis in these two patients and Table V shows the carbenicillin concentrations obtained in the peritoneal dialysis fluid and the corresponding peritoneal clearances of carbenicillin. In Case 5 there was a reduction in half-life from 6.7 hours without dialysis to 4.2 hours during peritoneal dialysis. In Case 4 the half-life was reduced from 23 hours without dialysis to 7.4 hours during peritoneal dialysis. The mean peritoneal clearance of carbenicillin in these two patients was 6.8 ml./min.

Side-effects.—None were observed during this study.

TABLE IV.—*Effect of Peritoneal Dialysis on Carbenicillin Levels*

Case No.	Dose	Serum Carbenicillin Levels (μg./ml.) During Peritoneal Dialysis					Half-life (Hours)
		Zero	1 Hr.	4 Hr.	8 Hr.	24 Hours	
4	1 g.	<3·0	115	97	63	13·7	7·4
5	1 g.	<3·0	82	42	36	—	4·2

TABLE V.—*Carbenicillin Concentrations in Peritoneal Dialysis Fluid with Corresponding Peritoneal Clearances of Carbenicillin for Four Consecutive Exchanges in Two Patients*

Case No.		Exchange Period			
		1	2	3	4
4	Carbenicillin conc. (μg./ml.)	29	34	47·5	28
	Peritoneal carbenicillin clearance (ml./min.)	6	8	12	6
5	Carbenicillin conc. (μg./ml.)	20	18	15	12
	Peritoneal carbenicillin clearance (ml./min.)	5	4	6	8

Discussion

The mean half-life of carbenicillin in those patients with endogenous creatinine clearances of less than 5 ml./min. was found to be 13.1 hours. There was, however, a wide range of from 6.7 to 23.5 hours. The mean serum level at one hour after the administration of 2 g. of carbenicillin intravenously was 207 μg./ml. To maintain serum carbenicillin levels of around 100 μg./ml., therefore, it would seem necessary to give 2 g. of carbenicillin intravenously every 8 to 12 hours. As the drug appears to be relatively free of side-effects, 2 g. of carbenicillin intravenously every eight hours might be employed.

During haemodialysis with the two-layer Kiil dialyser and using cuprophane membrane PT150, the half-life of carbenicillin in three patients was reduced. During haemodialysis, therefore, carbenicillin should be given at more frequent intervals and 2 g. intravenously every four hours is suggested.

The peritoneal clearance of carbenicillin was poor, with a mean clearance of 6.8 ml./min., though there was a reduction in half-life of from 6.7 to 4.2 hours in one patient and from 23 to 7.4 hours in another during peritoneal dialysis. During peritoneal dialysis 2 g. of carbenicillin intravenously every six hours is suggested.

Summary

The serum half-life of carbenicillin in patients with severe renal failure was determined. The mean serum half-life in eight patients was 12.5 hours.

Haemodialysis with the two-layer Kiil dialyser and using cuprophane membrane PT150 produced a reduction in half-life in three patients.

Peritoneal clearance of carbenicillin was poor, with a mean clearance of 6.8 ml./min. in two patients.

To maintain serum carbenicillin levels of around 100 μg./ml. in patients with severe renal failure—that is, endogenous creatinine clearance of <5 ml./min.—a dosage schedule of 2 g. intravenously every eight hours is suggested. This regimen requires some modification during haemodialysis or peritoneal dialysis.

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Preliminary Communications

Adrenergic Myenteric Nerves in Hirschsprung's Disease

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The clinical picture of Hirschsprung's disease is due to disordered function of a segment of colon and rectum. The histological abnormalities of this segment are an absence of myenteric ganglion cells and the presence of large abnormal nerve trunks (Whitehouse and Kernohan, 1948). These nerve trunks give a strong acetylcholinesterase staining reaction (Kamijo *et al.*, 1953). The myenteric ganglia are usually accepted as part of the parasympathetic system, and their absence may account for the disordered peristalsis in Hirschsprung's disease. It has also been suggested that a deficient adrenergic innervation might be responsible for the contracted state of the affected bowel (Kamijo *et al.*, 1953 ; Wright and Shepherd, 1965). In the present study we have tested this possibility using the catecholamine fluorescence technique of Falck and Hillarp (Falck, 1962).

METHOD

The abnormal bowel was resected because of Hirschsprung's disease in five children aged from 4 months to 3¾ years. Normal control specimens were obtained from two children, aged 11 and 15 months, whose lower bowel (including the rectum from one) had been resected for other reasons. Small full-thickness pieces of gut from different levels of each resected specimen were rapidly frozen, freeze-dried, and treated with formaldehyde gas as described by Falck and Owman (1965).