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Serum ciprofloxacin concentrations in patients with severe sepsis being treated with ciprofloxacin 200 mg iv bd irrespective of renal function

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Introduction

The dosing of ciprofloxacin in renal impairment has been debated since the late 1980s (Fillastre *et al.*, 1987). Basing their recommendations on a single iv dose of ciprofloxacin 100 mg or 200 mg iv Webb *et al.* (1986) and Drusano *et al.* (1987) recommended dose reductions in patients with reduced creatinine clearances. Similarly for oral therapy Boelaert *et al.* (1985) suggested a dose reduction with severe renal impairment. Others, in contrast, have shown no correlation between serum elimination half-life and creatinine clearance for patients treated with ciprofloxacin 200–300 mg iv (Bindschedler *et al.*, 1988). When ciprofloxacin was launched in the UK in 1987 there were few data on the expected serum concentrations after multiple dosing in patients with renal impairment and severe sepsis. This information is particularly important in view of the relationship of serum concentrations or the serum area under the curve and pathogen MIC to infection outcome, as suggested by Nix *et al.* (1987) and subsequently extended and consolidated for ITU pneumonia by Peloquin *et al.* (1989). We have recommended the use of ciprofloxacin 200 mg iv bd in renal impairment and severe sepsis with serum level determinations since 1987 and have collected data on sixteen patients who form the basis of this short report.

Materials and methods

All the patients included were either in-patients at Southmead Hospital or the Bristol Royal Infirmary, Bristol, UK. The Medical Microbiologists on both sites advised on the management of the patients, all of whom had severe infection requiring parenteral therapy and many of whom required intensive care. All patients received the standard dosage of ciprofloxacin 200 mg bd iv which was not modified for the degree of renal impairment. Serum ciprofloxacin assays were performed by HPLC based on the method of Gau *et al.* (1985).

Results and discussion

The data from 16 patients were sufficiently complete to allow analysis, 13 males and three females, with a mean age of 47 years, range 19–79 (Table). Many of the patients were also receiving other antibiotics and medications in addition to ciprofloxacin.

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Table. Clinical features, renal function and serum ciprofloxacin concentrations in the patients studied

Age (y)	Sex	Serum creatinine (μmol/L)	Infective diagnosis	Aetiology	Underlying or previous conditions	No. of doses given before assays	Ciprofloxacin concentrations pre-dose (mg/L)	Ciprofloxacin concentrations 1 h post-dose (mg/L)
Group 1 serum creatinine < 120 μmol/L								
22	M	53	hospital acquired chest infection	unknown	viral encephalitis	4	< 0·1	1·1
44	M	78	osteomyelitis	*Salmonella heidelburg*	none	5	0·2	1·1
42	F	119	hospital acquired chest infection	mixed bacterial	chickenpox pneumonia	4	0·8	2·2
Group 2 serum creatinine > 120 μmol/L and no renal support								
56	M	152	hospital acquired chest infection	*P. aeruginosa*	post cardiac surgery	3	0·5	4·7
63	M	161	hospital acquired chest infection	*P. aeruginosa*	multiple trauma after accident	5	0·5	2·1
33	M	176	recurrent septicaemia	*Escherichia coli*	renal transplant	7	0·5	3·3
78	F	282	septicaemia after UTI	*Klebsiella oxytoca*	none	5	1·0	2·1
65	M	476	infective endocarditis	*Staphylococcus aureus*	acute liver and renal impairment	10	1·1	2·1
56	M	636	hospital acquired chest infection	unknown	unstable angina	2	< 0·1	0·8
Group 3 serum creatinine > 120 μmol/L and requiring renal support								
19	M	376	community acquired chest infection	unknown	none	4	0·3	1·2
56	M	418	hospital acquired chest infection	unknown	head injury	4	0·5	1·4
53	M	477	wound infection	mixed bacterial	aorta bifemoral bypass graft	3	0·7	1·3
17	M	539	unknown	unknown	meningococcal septicaemia	9	0·2	2·9
79	M	556	septicaemia	*P. aeruginosa*	post-cardiac surgery	8	0·7	3·9
42	M	689	hospital acquired chest infection	coliform	severe low limb cellulitis	8	0·5	2·6
33	F	834	septicaemia	*P. aeruginosa* and coagulase-negative *Staphylococcus*	end stage renal disease	4	0·6	0 8

Seven patients had hospital acquired chest infections, four bacteraemia or septicaemia, and a further four were infected with either *Pseudomonas aeruginosa* or Enterobacteriaceae. Almost all patients had underlying conditions (Table). For the purposes of analysis, they were divided into three groups: group 1 ($n = 3$) serum creatinine concentrations of < 120 μmol/L; group 2 ($n = 6$), those with serum creatinine concentrations of > 120 μmol/L but did not require renal support; group 3 ($n = 7$) those with serum creatinine concentrations > 120 μmol/L who did require renal support. The UK data sheet recommends a 50% dose reduction for ciprofloxacin if the serum creatinine is > 265 μmol/L or the creatinine clearance is < 20 mL/min, therefore we also analysed the serum concentrations using these criteria. Of those patients requiring renal support two patients received haemodialysis, two haemofiltration, two continuous arteriovenous haemodialysis and one patient peritoneal dialysis. The mean serum creatinine ± S.D., and pre-dose ciprofloxacin concentrations ± S.D. (with ranges) for the three groups were: group 1, 83 ± 27 μmol/L; and 0·3 ± 0·3 mg/L (range < 0·1–0·8); group 2, 314 ± 182 μmol/l and 0·6 ± 0·4 mg/L (range < 0·1–1·1); and group 3, 556 ± 118 μmol/L and 0·5 ± 0·2 mg/L (range 0·3–0·7). Those patients with serum creatinine concentrations of < 265 μm/L had a mean pre-dose ciprofloxacin concentration ± S.D. of 0·43 mg/L ± 0·22 (range < 0·1–0·8) and those > 265 μmol/L mean levels of 0·57 ± 0·31 (range < 0·1–1·1).

The Figure shows the plot of the estimated creatinine clearance, derived from serum creatinine, age, sex and weight, when available, versus serum pre-dose ciprofloxacin concentration No correlation could be found to link creatinine clearance calculated using age and sex or age, weight and sex to pre-dose ciprofloxacin concentrations [$r^2 = 0{\cdot}1533$ ($n = 23$) and $r^2 = 0{\cdot}1859$ ($n = 17$)]. Post-dose serum concentrations measured 1 h after the end of the infusion and were variable with a mean of 2·1 ± 1·1 mg/L and range of 0·8–4·7 mg/L. Most of the serum ciprofloxacin assays were performed round the fourth to sixth dose.

Our data indicate that ciprofloxacin 200 mg bd given to patients with moderate to severe renal impairment does not accumulate. Serum concentrations are broadly similar to those found by others in patients with serious infection (Scully & Neu, 1987).

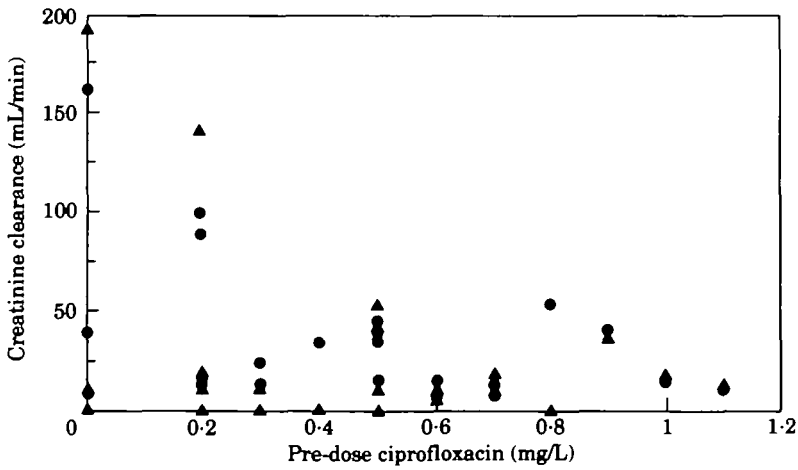

Figure. Creatinine clearance plotted against pre-dose serum ciprofloxacin concentrations. ●, Age and sex; ▲, age, weight and sex.

There was no correlation between serum ciprofloxacin concentration and renal function in our patients with severe sepsis, but, both pre-dose and post-dose levels were noted to be highly variable In our view dosage modification is not required when iv ciprofloxacin is used to treat severe infections in patients with moderate or severe impairment of renal functions. Furthermore, if the dosage is reduced our data would suggest that sub-therapeutic levels may occur. In renal impairment compensatory trans-intestinal elimination of ciprofloxacin takes over from the kidneys (Rohwedder *et al.*, 1990). However, treatment outcome depends on antibiotic concentration and bacterial susceptibility to ciprofloxacin. Because of the great variability in serum concentrations serum monitoring is required to enable therapy to be optimized for an individual patient (Peloquin *et al.*, 1989). It is likely that in the future 400 mg bd will become the standard parenteral ciprofloxacin dose but the kinetics of this larger dose in those with severe infection and renal impairment will need to be established.

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