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The pharmacokinetics of intravenous ciprofloxacin 400 mg 12 hourly in patients with severe sepsis: the effect of renal function and intra-abdominal disease

E. M. Jones*, C. M. McMullin, A. J. Hedges, A. M. Lovering, L. O. White, D. S. Reeves and A. P. MacGowan

Bristol Centre for Antimicrobial Research and Evaluation, Southmead Health Services NHS Trust and the University of Bristol, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, UK

Serum concentrations of ciprofloxacin were reviewed in 22 patients given ciprofloxacin 400 mg intravenously 12 hourly for severe infection. No dosage modifications were made in patients with renal impairment. Patients who had either bowel or liver pathology in addition to renal failure had significantly higher serum concentrations than all other patients. Dosage reduction of ciprofloxacin in patients with severe sepsis and impaired renal function is not required unless they have co-existent intra-abdominal disease.

Introduction

As the tenth anniversary of its UK launch approaches, the indications for ciprofloxacin use have widened and the dosages used increased. For example, in severe sepsis involving ICU patients in our hospital, a dosage of 400 mg iv bd is now routine. However, the debate over dosage modifications in renal failure continues. Dosage reduction of 50% has been recommended in severe renal failure both for oral doses[1,2] and for iv doses of 100 mg and 200 mg.[3,4] The current UK data sheet recommends a 50% dosage reduction if the serum creatinine is >265 μmol/L or the creatinine clearance (CrCl) is <20 mL/min. However, Brindschedler *et al.*[5] and Dirksen *et al.*[6] found no correlation between CrCl and renal clearance of ciprofloxacin and, in a previous study of 16 patients receiving iv ciprofloxacin 200 mg bd, MacGowan *et al.*[7] found no correlation between the CrCl and pre-dose ciprofloxacin concentrations. These findings can be explained by increased transintestinal elimination of ciprofloxacin[8] compensating for the reduced renal elimination seen in renal failure. We have, therefore, continued to use ciprofloxacin without dosage modification to treat patients with severe sepsis and renal failure. So far relatively few data on the use of iv ciprofloxacin 400 mg bd are available, but Shah *et al.*[9] reported that at this higher dose the CrCl could be correlated with pre-dose serum ciprofloxacin concentrations and that dosage modification is indicated. We report here a study of ciprofloxacin pharmacokinetics in 22 patients in an intensive care unit (ICU) who received iv ciprofloxacin 400 mg bd to treat known or suspected severe bacterial infection.

Materials and methods

All patients included in this survey were inpatients on the ICU at Southmead Hospital, Bristol, UK. All patients required parenteral therapy and received iv ciprofloxacin 400 mg bd unmodified for the degree of renal impairment. Any dosage modifications were made on the basis of ciprofloxacin serum concentration. Serum ciprofloxacin assays were performed by HPLC.

Results and discussion

The data from 22 patients were available for analysis, 13 males and nine females. The mean age was 60 years, range 29–76 years (Table). Many of the patients received other antibiotics in addition to ciprofloxacin. Ten of the patients had septicaemia, four had community-acquired chest infections, three hospital-acquired chest infections and three had intra-abdominal sepsis. Almost all had underlying conditions for which they had initially been admitted. For the purpose of analysis they were divided into four groups: group 1 (n = 5) had serum creatinine concentrations of <120 μmol/L; group 2 (n = 4) had serum creatinine concentrations >120 μmol/L but did not require renal support; group 3 (n = 5) required renal support but had no intra-abdominal disease; group 4 (n = 8) required renal

*Tel: +44-117-950-5050; Fax: +44-117-959-3154; E-mail: lesassays@ukneqasaa.win-uk.net

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

Patient no.	Age (years)	Sex	Serum creatinine (μmol/L)	Infective diagnosis	Aetiology	Underlying condition	No. of doses given before assay	Ciprofloxacin concentration (mg/L) pre-dose	Ciprofloxacin concentration (mg/L) 1 h post-dose	Bowel pathology	Bilirubin (2–20 IU/L)
Group 1											
1	70	F	55	pneumonia	*Pseudomonas aeruginosa*	bronchiectasis	6	0.9	4.2	no	9
2	60	F	68	hospital-acquired chest-infection	unknown	overdose	7	0.8	3	no	12
3	60	M	80	severe wound infection	coliforms and pseudomonas	squamous cell carcinoma of tongue	4	0.1	1.8	no	8
4	29	M	85	community acquired chest infection	unknown	nil	10	0.3	2.6	no	33
5	48	F	117	septicaemia	*Acinetobacter* sp.	glioma	15	1.6	3.7	no	73
Group 2											
6	69	M	130	sepsis	unknown	ureteric carcinoma—operated	6	0.5	3.4	no	18
7	63	F	137	peritonitis	unknown	appendicitis—perforated	6	1	4	yes: peritonitis	12
8	57	M	170	sepsis—originating from renal tract?	unknown	renal/ureteric stones	1	1.8	4.3	no	68
9	65	M	317	sepsis	unknown	repaired aortic aneurysm	8	1.3	4.3	no	11
Group 3											
10	56	F	165	community-acquired chest infection	unknown	asthma	5	2.6	5	no	68
11	53	F	317	chest infection	*Streptococcus pneumoniae*	non-Hodgkin's lymphoma	1	2.6	6.4	no	33
12	72	M	501	post-operative sepsis	*Stenotrophomonas maltophilia*	ruptured and repaired aortic aneurysm	3	1.5	3.1	no	80
13	62	M	572	central line sepsis post-operatively	*Staphylococcus aureus*	leaking aortic aneurysm, operated	4	0.4	1.4	no	15
14	74	M	588	septicaemia	*Enterobacter* sp.	ruptured aortic aneurysm, operated	3	1.3	3.6	no	142
Group 4											
15	65	M	199	hospital-acquired chest infection	mixed bacterial	left ventricular thrombus with emboli	2	1.5	7.7	yes: infarcted gut	8
16	64	F	218	miliary tuberculosis and septicaemia	*Klebsiella aerogenes*		9	3.2	6	yes: TB peritonitis	220
17	76	M	235	sepsis and *Clostridium difficile* infection	unknown	fractured neck of femur	8	6.2	7.8	yes: *C. difficile* pseudomembranous colitis	17
18	69	M	286	post-operative intra-abdominal sepsis	unknown	carcinoma head of pancreas, operated	1	1.6	3.6	yes: peritonitis	140
19	71	F	116	post-operative intra-abdominal sepsis	unknown	carcinoma head of pancreas, operated	5	7.6	11.1	yes: peritonitis	416
20	44	F	463	hospital-acquired chest infection	unknown	subarachnoid haemorrhage	1	3.1	7.8	yes: coeliac disease	8
21	42	M	463	leptospirosis	*Leptospira interrogans*	nil	5	2.9	5.7	no	591
22	76	M	503	septicaemia secondary to UTI	*Escherichia coli*	nil	5	6.4	8.1	yes: severe diarrhoea	150

support and had intra-abdominal disease. Intra-abdominal disease was defined as bowel pathology (severe diarrhoea, gut infarction, pseudomembranous colitis, peritonitis, coeliac disease) or hyperbilirubinaemia (10 × the upper limit of normal) (Table). In groups 3 and 4 two patients were receiving haemodialysis and 11 haemofiltration.

The data were analysed by an unpaired *t*-test to assess whether there was a significant difference between the ciprofloxacin pre-dose concentrations in patients with normal renal function compared with those with renal impairment. The data were also re-analysed using the Tukey–Kramer method[10] in order to confirm our initial findings. The median (range) of the serum creatine and the median (range) of the pre-dose ciprofloxacin concentration, respectively, for the three groups were: group 1, 80 (55–117) μmol/L and 0.8 (0.1–1.6) mg/L; group 2, 153.5 (130–317) μmol/L and 1.15 (0.5–1.8) mg/L; group 3, 501 (165–588) μmol/L and 1.5 (0.4–2.6) mg/L; group 4, 260 (116–503) μmol/L and 3.15 (1.5–7.6) mg/L. The UK data sheet recommendations for reduced dosage in renal impairment are for patients with serum creatinine >265 μmol/L or CrCl of <20 mL/min. The median pre-dose ciprofloxacin concentration in patients with serum creatinine <265 μmol/L was 1.5 mg/L (range, 0.1–7.6 mg/L) and in those with a serum creatinine of >265 μmol/L the median pre-dose ciprofloxacin concentration was 1.6 mg/L (range, 0.4–6.4 mg/L). When creatinine clearance was calculated, patients with clearances <20 mL/min had a median pre-dose ciprofloxacin concentration of 2.6 mg/L (range, 0.4–6.4 mg/L) while those with clearances of >20 mL/min had a median pre-dose ciprofloxacin concentrations of 1.5 mg/L (range 0.1–7.6 mg/L).

No significant difference was demonstrable between the concentrations of ciprofloxacin in groups 1, 2 or 3, or between those with serum creatinine above or below 265 μmol/L or CrCl above or below 20 mL/min. When the patients, excluding those in group 4, were split into those patients not requiring renal support (group 1 + group 2, $n = 9$) and those who required renal support (group 3, $n = 5$), again there was no significant difference. The median (range) of the pre-dose ciprofloxacin concentration for the former group was 0.9 (0.1–1.8) mg/L and for the latter 1.5 (0.4–2.6) mg/L. A linear regression analysis was performed to assess the correlation between the estimated CrCl and the pre-dose ciprofloxacin concentration (Figure). No clinically significant correlation could be demonstrated ($r^2 = 0.13$; $n = 22$). A comparable finding for the iv ciprofloxacin 200 mg bd dosage has been described.[7]

A significant difference ($P < 0.01$) was, however, demonstrated between the ciprofloxacin concentrations in groups 1, 2 and 3 (median pre-dose ciprofloxacin concentration 1.15 mg/L, $n = 14$, range 0.1–2.6 mg/L) compared with group 4. There was no association between the number of doses of ciprofloxacin given before assay and the pre-dose concentration achieved ($r^2 < 0.1$; $n = 22$). There was only a weak correlation between serum bilirubin concentration and pre-dose ciprofloxacin concentrations ($r^2 = 0.23$; $n = 22$). Pre-dose and post-dose concentrations were correlated ($r^2 = 0.77$; $n = 22$) indicating that high post-dose ciprofloxacin concentrations (>7 mg/L, $n = 5$, all group 4) were due to accumulation. For those patients with pre-dose concentrations of ciprofloxacin > 6 mg/L a dose reduction was made resulting in the drug concentrations falling to more acceptable levels.

This study again supports the view that ciprofloxacin dosage modification on the basis of serum creatinine or CrCl may result in sub-therapeutic concentrations in certain patients. In addition the data underline the importance of transintestinal and biliary elimination of ciprofloxacin as a compensatory pathway for excretion of ciprofloxacin when renal impairment is present. In eight of our patients who had both renal impairment and intra-abdominal disease, high ciprofloxacin concentrations were seen. We, therefore, recommend the use of iv ciprofloxacin 400 mg bd without dosage modification in renal failure unless there is co-existent bowel pathology or a high bilirubin concentration. Consideration should then be given to dosage reduction but, if possible, this should be based on assays of serum ciprofloxacin concentrations, since these vary considerably between such patients.

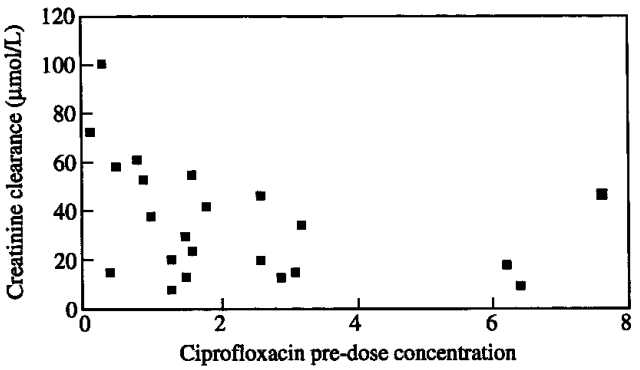

Figure. Creatinine clearance plotted against ciprofloxacin pre-dose concentration $r^2 = 0.13$.

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