Chronic dose urinary and serum pharmacokinetics of norfloxacin in the elderly

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1 Norfloxacin was administered as two daily 400 mg oral doses to eight elderly patients requiring treatment for urinary tract infections. Blood specimens were obtained for pharmacokinetic profiles following the first and fifteenth doses. Further specimens were obtained before each morning's dose of norfloxacin. Specimens of urine were obtained to ascertain if adequate antimicrobial concentrations were reached in these patients with diminished renal function.

2 Norfloxacin half-life was consistent with that expected in mild renal impairment and was not different between the first and fifteenth doses. Based on ratios of AUC values, accumulation is probably related to renal function, being greatest for creatinine clearance values below 30 ml min⁻¹.

3 On the great majority of occasions, the urinary concentrations of norfloxacin exceeded 20 µg ml⁻¹. On days 2-7, the mean percentage 12 h renal elimination of norfloxacin was 18.6 ± 1.47 (mean of 82 separate observations). Norfloxacin 400 mg twice daily was well tolerated in this group of elderly patients and produced adequate antimicrobial concentrations in urine.

Keywords norfloxacin pharmacokinetics urinary-concentrations elderly

Introduction

Norfloxacin is a 4-quinolone antimicrobial compound with high activity against a broad spectrum of bacteria pathogenic to humans (King *et al.*, 1982). *In vitro* studies have demonstrated inhibitory activity against common and uncommon urinary pathogens and clinical studies have demonstrated efficacy in treatment of urinary tract infections in hospital and in general practice (Deaney *et al.*, 1984; Guerra *et al.*, 1983).

Renal function falls as a function of age and may be associated with reduced renal elimination and urinary concentrations of drugs in elderly people. In the case of antimicrobial agents this could potentially cause subtherapeutic concentrations in urine with resulting infections due to multiply resistant bacteria or in acquisition of antibiotic resistance by the infecting bacteria.

Because of the possible consequences of reduced renal elimination of antibiotics used in the

treatment of urinary tract infections, determination of their pharmacokinetic characteristics is essential to understanding their therapeutic utility in the elderly.

Methods

Eight elderly female inpatients, requiring treatment for urinary tract infections received norfloxacin. The study was approved by the relevant Hospital Ethics Committee and informed consent was obtained. None had a history of any drug allergy or any acute renal, hepatic, or gastrointestinal disease. None was receiving or had received in the previous 5 days, any systemic antimicrobial therapy or antacid preparations.

Each person received one 400 mg tablet of

norfloxacin with a glass of water, every 12 h, for 15 doses. On the morning of the first and eighth days, the pre-dose urine was collected and a blood specimen obtained. Further blood specimens were obtained at 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h following norfloxacin administration. Urine was collected for the following time intervals, 0–3, 3–6, 6–9, 9–12 and 12–24 h on the first and eighth days. Following the last dose, urine was collected for the period 24–48 h. On the remaining study days, a pre-morning dose blood specimen was obtained and urine was collected for the periods 0–12 and 12–24 h following the morning doses. Blood was allowed to clot in a plain glass tube, centrifuged and the serum removed and stored at -20°C until required for norfloxacin assay. The volume and pH of urine specimens were recorded and 20 ml aliquots stored as for serum.

Norfloxacin concentrations in serum and urine were estimated by a high performance liquid chromatography method similar to that of Boppana & Swanson (1982) except for the use of a reversed phase column (Spherisorb 5ODS, 15 cm $\times$ 5 mm i.d.). The mobile phase was a mixture of 300 ml methanol, and 700 ml of a solution containing 1.74 g KH_2PO_4 , 20 mg hexane sulphonic acid and 1 ml 85% phosphoric acid. The chromatography flow rate was 2 ml min^{-1} . Typical retention times were 3 min for norfloxacin and 4.5 min for the pipemidic acid internal standard. The inter-assay variability (coefficient of variation) was 5.2% at $0.82\text{ }\mu\text{g ml}^{-1}$ norfloxacin in serum ($n = 6$) and 7.3% at $81\text{ }\mu\text{g ml}^{-1}$ norfloxacin in urine ($n = 7$).

Results

Eight patients aged between 73 and 94 years entered the study. All patients were female, within the weight range of 42–68 kg. Renal function was determined from creatinine clearance and varied from 27–62 ml min^{-1} . Details of the eight patients are shown in Table 1. All patients had cultures positive for *Escherichia coli* and one (LK) was also positive for *Streptococcus faecalis*.

No adverse reactions were reported during the study and the urinary tract infection resolved in each case, based on clinical findings and a negative culture within 1 week of ending medication. Figure 1 shows mean values of serum norfloxacin concentrations at the various times on days 1 and 8 respectively. After the first dose, the maximum mean concentration was $1.36 \pm 0.24\text{ }\mu\text{g ml}^{-1}$, observed at 2 h. Individual maximum concentrations ranged from $0.77\text{--}2.29\text{ }\mu\text{g ml}^{-1}$ with a mean value of $1.62 \pm 0.18\text{ }\mu\text{g ml}^{-1}$.

Table 1 Demographic information

Subject	Age (years)	Sex	Weight (kg)	Creatinine clearance (ml min^{-1})
GS	94	F	46.5	31
NC	78	F	55.2	42
MM	79	F	44.6	62
AR	87	F	60.8	29
HL	73	F	68.0	53
LK	91	F	58.2	40
MT	89	F	42.0	42
MW	79	F	53.0	27

Table 2 Mean $\pm$ s.e. mean serum norfloxacin concentrations before each morning's dose

Day	Serum norfloxacin ($\mu\text{g ml}^{-1}$)
1	0
2	0.61 ± 0.15
3	0.66 ± 0.11
4	0.64 ± 0.13
5	0.84 ± 0.15
6	0.82 ± 0.13
7	0.62 ± 0.08
8	0.61 ± 0.13

Figure 1 Mean serum norfloxacin concentrations on days 1 (Δ) and 8 ($\bullet$).

After the 15th dose, maximum mean concentration was $1.66 \pm 0.32\text{ }\mu\text{g ml}^{-1}$, observed at 1.5 h. Individual maximum concentrations varied from $0.96\text{--}3.89\text{ }\mu\text{g ml}^{-1}$ with a mean of $2.05 \pm 0.37\text{ }\mu\text{g ml}^{-1}$. While the mean maximum concentration was slightly higher on day 15 than on day 1, the difference was not significant (Student's *t*-test for paired data). Mean values of half-life, calculated by least squares linear regression analysis of the terminal portions of the log concentrations-time profiles were $5.18 \pm 0.63\text{ h}$ after the first dose and $5.43 \pm 0.38\text{ h}$ after the last

dose (Table 3). These were not significantly different. The mean pre-dose norfloxacin serum concentrations were quite consistent and are shown in Table 2.

Values of areas under the serum concentration-time curves (calculated by the trapezoidal rule) are shown in Table 3. Values tended to be higher on day 8 but not in all cases. In two cases values of AUC were lower on day 8 than on day 1, presumably due to variation in absorption of norfloxacin. The mean ratio AUC day 8/AUC day 1 was 1.62 ± 0.35 but was variable. While there was no significant relationship between this ratio and creatinine clearance, there was a tendency towards larger ratios in patients with low values of creatinine clearance. Thus the two patients with creatinine clearance values below 30 ml min^{-1} had the highest AUC ratios (2.02 and 3.69). The mean value of the ratio for the remaining six was 1.24.

Table 4 shows the mean urinary norfloxacin concentrations over a dose interval, on days 1 and 8 at the various sampling times. Concentrations during days 2–7 were similar to these. In Figure 2 is shown the distribution of urinary

norfloxacin concentrations throughout the study period, including the period 12–48 h following the final norfloxacin dose. Less than 2% of observations were associated with values of concentration under $10 \mu\text{g ml}^{-1}$ and 5.5% of observations were associated with concentrations less than $20 \mu\text{g ml}^{-1}$. All but one of the concentrations under $10 \mu\text{g ml}^{-1}$ occurred more than 12 h following the final dose. Four of the 10 concentrations under values $20 \mu\text{g ml}^{-1}$ occurred more than 12 h following the final dose. Overall, the majority of urinary norfloxacin concentrations were in the range of $20\text{--}200 \mu\text{g ml}^{-1}$, and the majority of peak urinary norfloxacin concentrations were in excess of $200 \mu\text{g ml}^{-1}$.

The mean 12 h urinary elimination of norfloxacin was $17.7 \pm 4.41\%$ of the administered dose following the first dose ($n = 7$). Following the final dose $22.9 \pm 10.2\%$ of the administered dose was eliminated in 12 h (i.e. over a dose interval, $n = 6$). On days 2–7 the mean percentage 12 h urinary elimination of the administered dose was 18.6 ± 1.47 (mean of 82 separate 12 h observations). In some cases urine collections were incomplete and these values were not included in the above results.

Table 3 Values of AUC and half-life on the first and last days

Subject	AUC 0–12 ($\mu\text{g ml}^{-1} \text{ h}$)		Half-life (h)	
	Day 1	Day 8	Day 1	Day 8
GS	13.32	18.97	3.6	5.9
NC	9.03	14.38	4.9	5.2
MM	10.25	17.69	8.8	5.7
AR	13.00	26.30	5.7	7.3
HL	9.13	3.20	3.5	4.7
LK	6.27	8.95	4.1	3.5
MT	8.83	8.02	4.3	5.6
MW	5.13	18.96	6.5	5.5
Mean	9.37	14.56	5.18	5.43
s.d.	2.86	7.46	1.79	1.08
s.e. mean	1.01	2.64	0.63	0.38

Table 4 Urinary concentrations of norfloxacin during a dose interval on days 1 and 8

Collection period		Urinary norfloxacin ($\mu\text{g ml}^{-1}$)
Day 1	0–3 h	150 ± 62
	3–6 h	214 ± 60
	6–9 h	129 ± 38
	9–12 h	142 ± 72
Day 8	0–3 h	112 ± 29
	3–6 h	320 ± 64
	6–9 h	235 ± 62
	9–12 h	93 ± 28

Discussion

The mean values of half-life after the first dose (5.18 h) and the last dose (5.43 h) in these elderly people were longer than the values of around 3 h found by us on previous occasions and by others (Eandi *et al.*, 1983; Hughes *et al.*, 1984) in young people with normal renal function. Values were consistent with the half-life found in mild renal impairment. There was no significant relation-

Figure 2 Distribution of urinary concentrations of norfloxacin.

ship between norfloxacin elimination rate and creatinine clearance in these patients. Peak serum concentrations were higher on day 8 than on day 1 but not significantly so. Pre-dose concentrations were fairly consistent throughout the study with mean values in the approximate range of 0.6–0.8 $\mu\text{g ml}^{-1}$.

Values of AUC were variable, making accurate estimation of accumulation difficult. This is probably a reflection of variable absorption of norfloxacin. However, results for the two patients with creatinine clearance values less than 30 ml min^{-1} suggest that accumulation may become significant in this group. This is probably related to renal function, rather than primarily to old age.

Mean urinary concentrations in the 12 hourly urine collections on days 2–7 ranged from 81 to 222 $\mu\text{g ml}^{-1}$. Individual concentrations were generally greater than 20 $\mu\text{g ml}^{-1}$ and only on a very small number of occasions were values less than 10 $\mu\text{g ml}^{-1}$. Minimum inhibitory concen-

trations of norfloxacin (MIC 90, minimum concentrations required to kill 90% of organisms) have been shown to be 4 $\mu\text{g ml}^{-1}$ for both *Ps. aeruginosa* and *Strep. faecalis* and 0.25 $\mu\text{g ml}^{-1}$ for *E. coli* (Kahn *et al.*, 1982). It is evident that urinary concentrations of norfloxacin comfortably exceeded these concentrations in the great majority of cases.

In this group of elderly patients requiring antimicrobial treatment for urinary tract infections, administration of norfloxacin 400 mg twice daily resulted in satisfactory urinary concentrations of the drug. The half-life was slightly prolonged in relation to that expected in young people but nevertheless, peak serum concentrations were not notably higher after repeated-dose administration. Patients with moderate renal impairment (creatinine values less than 30 ml min^{-1}) would be expected to have accumulation ratio values higher than patients with mild or absent renal impairment.

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