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Communication

The pharmacokinetics of antofloxacin in renally impaired rats

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Abstract

Our aim was to investigate whether renal impairment induced by cisplatin altered the pharmacokinetics of antofloxacin. Antofloxacin (7.5 mg kg^{-1}, i.v.) was given to normal or renally impaired rats (induced by cisplatin). Concentrations of antofloxacin in plasma and urine were measured using HPLC. Pharmacokinetic parameters were estimated. The plasma concentrations of antofloxacin in the renally impaired rats were significantly higher than those in the normal rats, accompanied by significant increase of the area under the plasma concentration–time curve (AUC) (968.78 ± 259.39 μg min mL^{-1} versus 509.84 ± 46.19 μg min mL^{-1} in normal rats $P < 0.05$). The system clearance (CL) and renal clearance (CL_R) of antofloxacin decreased from 12.66 ± 1.15 mL kg^{-1} min^{-1} and 3.21 ± 1.80 mL kg^{-1} min^{-1} in normal rats, to 6.63 ± 2.82 mL kg^{-1} min^{-1} and 0.31 ± 0.15 mL kg^{-1} min^{-1}, respectively. No differences between two treatments in half-life and mean residence time were found. We concluded that renal impairment induced by cisplatin significantly altered the pharmacokinetics of antofloxacin and resulted in decrease of the renal elimination.

Introduction

Quinolones have been used increasingly widely in clinical practice, but their common adverse effects involving the gastrointestinal tract, skin and the central nervous system should be not neglected (Blondeau & Missaghi 2004; Owens & Ambrose 2005). Adverse effects including headaches, dizziness, seizures, phototoxicity and prolongation of depolarization have been described in patients treated with quinolones (Blondeau & Missaghi 2004; Owens & Ambrose 2005; Mehlhorn & Brown 2007).

The kidney is known to modulate the pharmacokinetics of various drugs, and most quinolones are primarily eliminated through the kidneys, which suggests that renal dysfunction might alter their pharmacokinetics. A report showed that the differences of pharmacokinetics in elderly versus younger adults were attributed to differences in renal function and not specifically to age (Owens & Ambrose 2005). Clinical practices demonstrated the adjustment in dosage of quinolones in patients with renal dysfunction (Dorr et al 1999; Ohtani et al 2006).

Antofloxacin hydrochloride is a newly developed active quinolone carboxylic acid and an 8-NH_2 derivative of levofloxacin (Figure 1). It is effective against aerobic and anaerobic Gram-positive and Gram-negative bacteria, and exhibits antibacterial activity markedly superior to levofloxacin, from which it is derived, against *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Ye et al 2002). It has been licensed recently for the treatment of respiratory tract and urinary tract infection in China.

The aim of the study was to determine whether renal impairment affected the pharmacokinetics of antofloxacin using renally impaired rats induced by cisplatin.

Materials and Methods

Materials

Antofloxacin (purity > 99%) was obtained from Anhui Global Pharmaceutical Co. Ltd (Anhui, China). Gatifloxacin and lomefloxacin were purchased from National Institute

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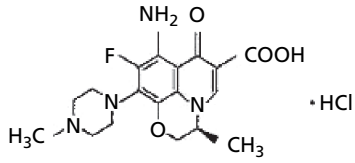

Figure 1 Structure of antofloxacin hydrochloride.

for the Control of Pharmaceutical and Biological Products (Beijing, China). Cisplatin for injection was produced by Qilu Pharmaceutical Co. Ltd. Creatinine reagent kit, nitrogen reagent kit, and Coomassie brilliant blue reagent kit were purchased from Nanjing Jiancheng Bioengineering Institute. Other reagents were of analytical grade and commercially available.

Animal studies

Male Sprague–Dawley rats, 238 ± 15 g, were purchased from Sino-British Sippr/BK Lab Animal Ltd (Shanghai, China). The rats were housed under controlled environmental conditions (temperature, 23 ± 1°C; humidity, 55 ± 5%) and fed standard laboratory chow with free access to water.

All animal experiments were performed in accordance with institutional guidelines for the care and the use of laboratory animals and approved by the Animal Ethics Committee of China Pharmaceutical University.

Establishment and verification of cisplatin-induced acute renal impairment

Twelve rats were divided into two groups; one was the control and the other was the cisplatin-exposed group. The rats intraperitoneally received single-dose cisplatin (8 mg kg^{-1}) or normal saline, respectively. Blood and urine samples were obtained at designated times. Two rats from each group were randomly selected and sacrificed on the fifth and ninth day following injection. Renal impairment was assessed by blood urea nitrogen, plasma creatinine, urine creatinine and urine total protein, which were measured using corresponding diagnostic kits. The kidney was obtained for histological assessment. Kidney was sectioned (5–6 μm) following being fixed in 10% formalin, dehydrated and embedded in paraffin. Sections were routinely stained with haematoxylin and eosin and assessed under a light microscope (Nikon E600).

Pharmacokinetic study

Ten rats were randomly divided into two groups—a control group, which received normal saline and the cisplatin-exposed (CI) group, which received a single dose of cisplatin (8 mg kg^{-1}, i.p). All the animal experiments were conducted on day 5 after administration of cisplatin or vehicle. The rats, following fasting overnight, intravenously received antofloxacin (7.5 mg kg^{-1}) and were housed individually in a metabolic cage with free access to water.

The blood samples (about 0.24 mL) were collected into heparinized tubes from the post-orbital venous plexus veins at 2, 20, 40, 60, 90, 120, 180, 240, 360, 480 and 720 min post administration and centrifuged at 8000 rev min^{-1} for 5 min at 10°C, and plasma samples were obtained and stored at −20°C until assay.

Urine samples were collected at 0–6, 6–12, 12–24 and 24–36 h intervals after the doses and the volume of urine was measured immediately, and 2 mL of urine was stored at −20°C until assay.

The concentration of antofloxacin in plasma and urine was measured by HPLC method with UV detection (Hu et al 2006; Pang et al 2007). The calibration curve from the standard samples was linear over the concentration range of 0.05–10 mg L^{-1} for plasma, and 0.2–50 mg L^{-1} for urine, respectively. The limits of the quantification in plasma and urine were 0.05 and 0.2 mg L^{-1}, respectively. Quality control samples produced from blank plasma and urine spiked with known concentration at three levels (high, medium and low) were stored and analysed together with study samples. Inter-day precision and accuracy were always well within the desired limits.

Pharmacokinetics analysis

The area under the plasma concentration–time curve (AUC) was calculated using the linear trapezoidal method. The mean residence time (MRT) was calculated by area under the first moment of the plasma drug concentration–time curve divided by AUC. The terminal elimination constant (λ_z) was calculated by log-linear regression of the last data points of the concentration–time profile and the terminal elimination half-life (t½) was obtained as $0.693/\lambda_z$. Systemic clearance (CL) was derived as dose divided by AUC and renal clearance (CL_R) was defined to be CRFE (cumulative renal fractional excretion at 36 h) multiplied by CL. Non-renal plasma clearance (CL_{nR}) was calculated by CL minus CL_R.

Statistical analysis

Results were expressed as means ± standard deviation. Differences between two treatments were examined using non-parametric test (Mann-Whitney method).

Results

Effect of cisplatin on kidney function

The urine concentration of total protein and the plasma concentration of urea nitrogen and creatinine were measured to assess the renal function in rats. Urine total protein concentration, blood urea nitrogen (BUN) and plasma creatinine concentration in the renally impaired rats were measured and peaks occurred on the fifth day following the dose of cisplatin. On day 5, the concentrations were measured to be 3.98 g L^{-1}, 26.58 mmol L^{-1} and 531.38 μmol L^{-1}, respectively, which were significantly higher than those (1.55 g L^{-1}, 2.90 mmol L^{-1}, 39.15 μmol L^{-1}, respectively) in normal rats. The biomarkers on day 5 reflected the severe syndrome of acute renal impairment, and thus the acute renal failure (ARF) model of 5 days was chosen to conduct the experiments.

Histology

Compared with the kidney of control rats, the rats exposed to cisplatin showed histopathological changes in the renal tubules and glomeruli. Degeneration of epithelia of renal tubules, as well as hyperaemia of the medullary and cortical parts with inflammatory cell infiltrates, was evident in the rats treated with cisplatin. A few renal tubules showed single epithelial cells desquamated to their lumen. Some tubules were obstructed by protein casts.

Pharmacokinetics of antofloxacin in the normal or renally impaired rat

The mean plasma concentration–time profiles of antofloxacin in the normal or renally impaired rats were evaluated (Figure 2). Pharmacokinetic parameters of antofloxacin were estimated (Table 1). The CRFE was also measured (Table 1).

Significantly higher plasma concentrations of antofloxacin in the renally impaired rats induced by cisplatin were found, resulting in a 1.9-fold increase in AUC and decrease in CL by 47.63%. The CRFE of antofloxacin in the renally impaired rat was lower than in normal rats (4.61 ± 1.40% in renally impaired rats vs 24.54 ± 12.6% in normal rats). The results showed that the decrease in CL mainly resulted from CL_R decrease, which was 9.66% that in normal rats. Exposure to cisplatin may also decrease CL_{nR} by 33.02%. However, cisplatin-induced renal impairment did not alter the t½ or MRT.

Discussion

This study demonstrated that cisplatin-induced renal impairment substantially altered the pharmacokinetics of antofloxacin in rats, resulting in higher plasma concentration and exposure, and lower CL values. Significantly higher values of AUC in the renally impaired rats reflected higher exposure of drug, accompanied by a decrease in CL. The reduction in CL in the renally impaired rats seemed to be due to the renal excretion and non-renal factors in consideration of the toxicity of cisplatin. The degree of CL_R decrease was larger than that of CL_{nR}, indicating that the higher exposure mainly resulted from decrease of clearance from kidney (CL_R), via impairment of kidney function.

Table 1 Pharmacokinetic parameters of antofloxacin following an intravenous (7.5 mg kg^{-1}) administration of antofloxacin to rats (mean ± s.d., n = 5)

Parameters	Normal rats	Cisplatin-exposed rats	*P*
t½ (min)	436.55 ± 110.51	451.46 ± 161.47	0.818
MRT (min)	319.74 ± 49.26	468.26 ± 201.18	0.180
AUC_{0-t} (μg min ml^{-1})	509.84 ± 46.19	968.78 ± 259.39*	0.004
$AUC_{0-\infty}$ (μg min ml^{-1})	596.98 ± 59.58	1279.46 ± 444.46*	0.004
CL (ml kg^{-1} min^{-1})	12.66 ± 1.15	6.63 ± 2.82*	0.004
CL_R (ml kg^{-1} min^{-1})	3.21 ± 1.80	0.31 ± 0.15*	0.002
CL_{nR} (ml kg^{-1} min^{-1})	9.45 ± 0.99	6.33 ± 2.69	0.065
CRFE (%)	24.54 ± 12.63	4.61 ± 1.40*	0.002

*Significantly different from normal rats ($P < 0.01$).

It is clear that the transporters located in the kidney of rats include organic anion transporter (OAT), organic cation transporter (OCT), peptide transporter and primary active transporter (Mizuno et al 2003). Also, antofloxacin is a zwitterion compound with both an amino group and a carboxyl group as other quinolone drugs, levofloxacin and ciprofloxacin, which are the substrates of OAT and OCT (Wada et al 2000; Bauer et al 2005). This indicates that antofloxacin may also be a substrate of OAT and OCT. Our previous study showed that the OAT inhibitor diclofenac acid may increase the AUC of antofloxacin, accompanied by a decrease in CRFE (Pang et al 2007). There are several reports (Deguchi et al 2005; Kwon et al 2007) about the alteration of OAT or OCT in the renal dysfunction state in man or the rat. Some reports show that cisplatin mainly induces necrosis or apoptosis of tubular cells in the kidneys (Liu & Baliga 2003; Tsuruya et al 2003; Arany et al 2004; Li et al 2004; Sheikh-Hamad et al 2004; Baek et al 2006). All the results indicate that alteration of antofloxacin CL_R in the renally impaired rat may be partly due to the decline of OAT or OCT as the excretion of *p*-aminohippurate reported (Owens & Ambrose 2005).

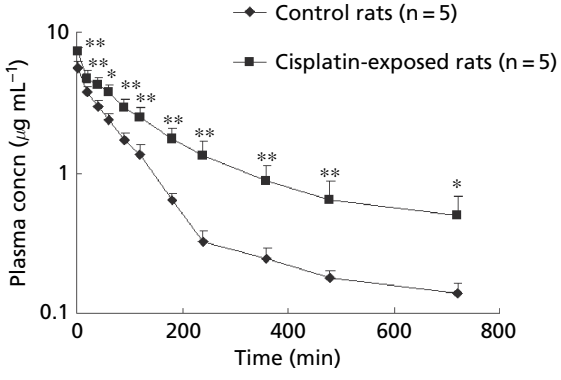

Figure 2 Plasma concentration vs time profiles of antofloxacin following single 7.5 mg kg^{-1} intravenous doses. Data are means ± s.d., n = 5. *$P < 0.05$, **$P < 0.01$ compared with control.

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