Review Article

Clinical Role of an Injectable New Quinolone Antibiotic, Pazufloxacine Mesilate

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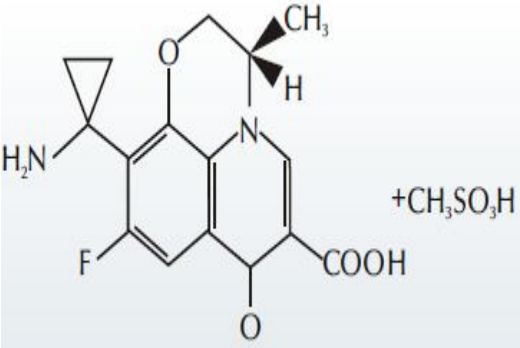
ABSTRACT

Pazufloxacin mesilate (PZFX) is an injectable new-quinolone antibiotic having 1-amino cyclo propyl group. It has been seen in basic studies that PZFX shows high blood concentration after intravenous administration and has weak actions such as convulsion-inducing action, local irritation action and hypotensive action etc. that are feared to develop in injectable new-quinolone group antibiotics. On the other hand, PZFX shows strong antibacterial strength even against bacteria that show resistance to cephem group, carbapenem group and amino glycoside group antibacterial drugs. An excellent therapeutic effect as compared to the known injectable cephem group antibacterial drugs was exhibited in animal infection test model with various types of resistant strains due to its strong bactericidal action. Furthermore, even in clinical tests conducted using injectable antibacterial drugs as subjects; PZFX showed clinical efficacy and safety same as injectable cephem group antibacterial drug ceftazidime (CAZ) in infection of more than medium severity. In addition to this, it showed satisfactory clinical efficacy even in cases of different areas that did not respond to previous medication[1]. PZFX is anticipated as a choice useful for treatment of bacterial infection from these basic test and clinical test results. In this review, clinical role of PZFX in the injectable antibacterial drugs is considered by explaining the basic and clinical results of PZFX.

INTRODUCTION

New-quinolone group antibacterial drugs show strong antibacterial activity and broad antibacterial spectrum against gram positive and gram negative bacteria based on stopping replication of DNA by acting on bacteria-specific DNA topoisomerase. Moreover, it does not show cross-over resistance with known antibacterial drugs such as b-lactam group antibacterial drugs that are generally used in the treatment of infection due to different action mechanism. It has strong concentration-dependent bactericidal action and furthermore, shows postantibiotic effect (PAE) against various types of bacteria due to which effect of inhibiting re-propagation of bacteria even after drug concentration in blood lowers below MIC, is anticipated. Moreover, it also has the advantage of showing efficacy in intracellular parasitic microbial infection with high tissue concentration as compared to blood concentration with satisfactory migration into tissue cells.

PZFX was developed by targeting on “new type of new-quinolone antibacterial drug having expanded safety region than the existing new-quinolone antibacterial drugs, with less effect on central nervous system even if blood concentration is increased, and in which high blood concentration is obtained quickly after intravenous administration[2]”.



Structure of pazufloxacin

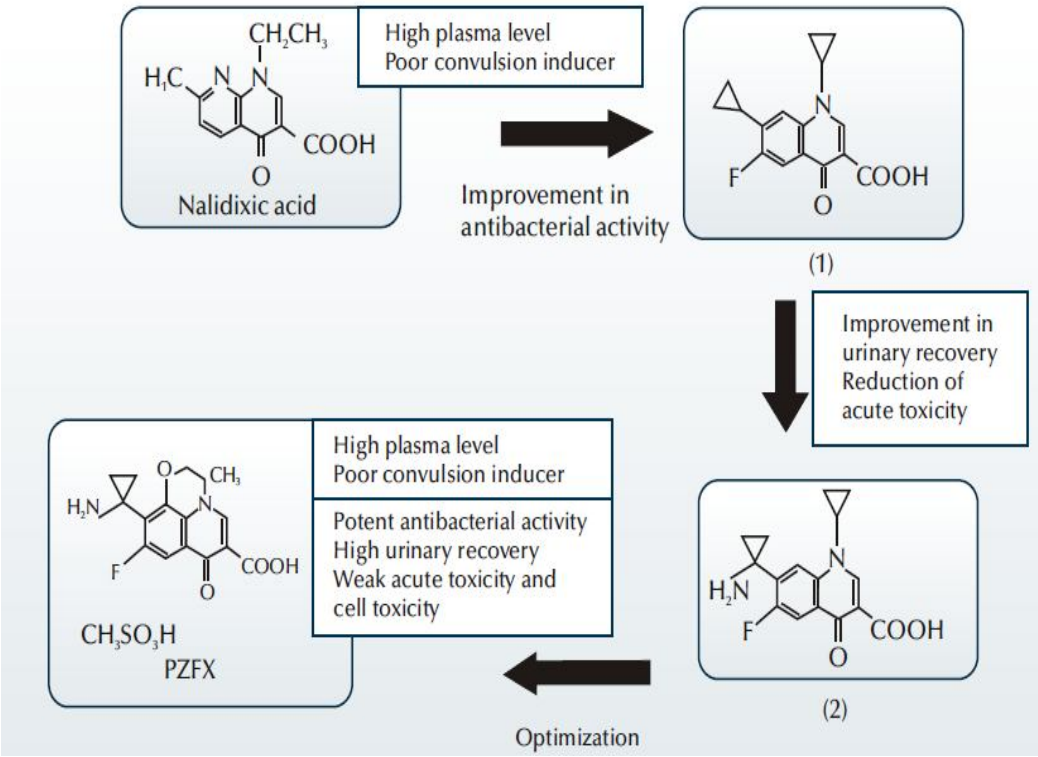
PZFX showed satisfactory therapeutic effect with weak convulsion-inducing action, while exhibiting high blood concentration after intravenous administration based on inserting a new 1 – amino cyclo propyl group via C – C (carbon – carbon bond) that is not seen in the existing new quinolone antibacterial drugs Moreover, basic advantages related to efficacy and safeties of PZFX have been confirmed

even in clinical tests at the time of development.

COURSE OF DISCOVERY

PZFX was actually discovered while focusing on high blood concentration by single oral administration and weak convulsion-inducing action and GABA receptor biding inhibition action by intracerebral administration in mice, seen in nalidixic acid (NA) which is the prototype of quinolone group antibacterial drugs, as compared to new-quinolone antibacterial drugs. When chemical structure of NA is compared with the known new-quinolone antibacterial drugs, it is found that pattern of bonding with side chain occurring at 7-position of NA is C – CH (carbon – carbon bond) while in the known new-quinolone 3 antibacterial drugs, it is C – N (carbon – nitrogen bond)

Therefore, side chain was studied focusing on relationship between the pattern of bonding of 7-position side chain and central nervous system and compounds having strong antibacterial activity, showing high blood concentration by intravenous administration and weak toxicity such as acute toxicity or convulsion inducing action etc. were searched. The flow of search has been shown in figure 3. A compound (1) in which naphthyridine of NA mother nucleus is changed to quinoline, fluorine is inserted at its 6 position and various alkyl groups or cyclo alkyl groups are inserted as 7-position side chain (1) was synthesized[3]. As a result, antibacterial activity improved to the extent same as that of the known new-quinolone antibacterial drugs however urine recovery rate lowered (assumed to get easily metabolized) and acute toxicity became stronger due to which substitution groups were further modified and 1-amino cyclo propyl group was inserted at 7th position. This compound (2) had satisfactory pharmacokinetics in mice (blood concentration by intravenous administration, migration to brain and urine recovery rate) and convulsion-inducing action (intracerebral administration) and acute toxicity (intravenous administration) were also improved[4]. Further optimization was performed and compound in which oxazine ring was inserted, showed strong antibacterial activity and broad antibacterial spectrum matching with those of CPFX and OFLX and showed high blood concentration by intravenous administration. Moreover, this compound had weak convulsion-inducing action, acute toxicity and cell toxicity than CPFX and OFLX, with increased selectivity in bacteria-specific DNA gyrase and topoisomerase II inhibition action of mammals such as humans.



PHARMACOLOGICAL ACTION

(1) Antibacterial activity against various types of clinical isolates

PZFX shows antibacterial activity against broad range of pathogenic microbes such as various gram positive and negative bacteria, acid-fast bacteria, mycoplasma, rickettsia etc. and satisfactory effect is obtained even against various types of resistant strains. The details have been given below.

1) Antibacterial activity against aerobic and facultative anaerobic bacteria

MIC of PZFX against gram positive bacteria except various types of resistant bacteria is 0.2 ~ 6.25 mg/mL while 50 MIC is 0.2 ~ 100 g/mL. MIC of PZFX against various gram negative bacteria is £ 0.05 ~ 0.78 mg/mL while MIC is 80 50 80 £ 0.05 ~ 25 g/mL. Strains having high resistance to this drug (MIC³100 mg/mL) were observed to be more than 10% in *Enterococcus faecalis* (30.2%), *Enterococcus faecium* (20.8%) and *Pseudomonas aeruginosa* (13.7%). However, it was less than 10 % in other species[5].

2) Antibacterial activity against anaerobic bacteria

MIC and MIC of PZFX against *Bacteroides fragilis* are both 6.25 mg/mL and MIC and MIC of PZFX against 50 80 50 80 *Prevotella species* is 1.56 mg/mL and 6.25 mg/mL respectively. The proportion of strains highly resistant to this drug belonging to *B. fragilis* and *Prevotella species* (MIC ³ 100 mg/mL) is less than 10.0 %.

3) Antibacterial activity against acid-fast bacteria and mycoplasma

MIC and MIC of PZFX against acid-fast bacteria including tuberculosis bacteria and mycoplasma is 50 90 4 ~ 16 mg/mL and 4 ~ 64 mg/mL[6].

PHARMACOKINETICS

(1) Blood concentration in humans

Highest blood concentration (Cmax) after 500 mg intravenous drip which is the single administration quantity for an adult showed high value of 11.0 mg/mL. Cmax and AUC at the time of single administration of 300 mg of CPFX as injection (single dosage quantity for adults) which belongs to the same family of injectable antibacterial drug in Japan is 3.33 mg/mL and 7.49 mg/hr/mL respectively as per enclosed literature. Cmax and AUC at the time of administration of 500 mg of this drug as intravenous drip was approximately 3 times that of CPFX injection.

(2) Migration into human tissue

Tissue migration of this drug is as follows. Satisfactory tissue migration was observed.

Sputum, lung tissue

Maximum sputum concentration at the time of single administration of 500 mg as intravenous drip for 30 minutes was 2.49 ~ 6.24 mg/g (n =4) 0.5 ~ 2.5 hours after starting the drip and moreover, lung tissue concentration 1.5 hours after starting the drip was average 7.95 mg/g (n = 5).

Biliary tract

Bile concentration in bile duct at the time of single administration of 500 mg as intravenous drip for 30 minutes was 5.47 ~ 29.9 mg/mL (n = 3) 1.5 ~ 4.5 hours after starting the drip while gall bladder tissue concentration 1.0 ~ 2.5 hours after administration was 9.85~ 35.5 mg/g (n = 4).

Pleural effusion, ascitic fluid

Pleural fluid concentration at the time of single administration of 500 mg as intravenous drip for 60 minutes was 1.43 mg/mL (n = 1) 7 hours after starting the drip while ascitic fluid concentration at the time of single administration of 300 mg as intravenous drip for 60 minutes was 1.87 mg/g (n = 1) 4 hours after starting the drip[8].

Wound pus and burnt skin tissue

Wound pus concentration at the time of single administration of 500 mg as intravenous drip for 30 minutes was average 4.73 mg/mL in 2 cases 1.5 hours after starting the drip while concentration of scar part of burnt skin tissue was average of 4.54 mg/mL in 4 cases 1.5 hours after starting the drip.

Female genital tissue

Concentration in different tissues of female reproductive system at the time of single administration of 300 mg as intravenous drip for 30 minutes was 5.00~13.9 mg/mL (n = 5) 0.83 hours after starting the drip while pelvic dead space fluid concentration was average of 3.18 mg/mL (n = 4) 2 hours after starting the drip.

Spinal fluid

Spinal fluid concentration at the time of single administration of 500 mg as intravenous drip for 30 minutes was average 0.33 mg/mL in 3 cases after 1.5 hours.

ANTIBACTRIAL ACTIVITY OF PZFX IN CLINICAL ISOLATES

Organism	Drugs	MIC (µg/mL)*			
		Range	50%	80%	90%
Moraxella catarrhalis	PZFX	≤0.05 - 0.2	≤0.05	0.1	0.1
	CAZ	≤0.05 - 0.39	0.1	0.1	0.2
	IPM	≤0.05 - 0.2	0.1	0.2	0.2
	GM	≤0.05 - 0.78	0.39	0.39	0.39
	CPFX	≤0.05 - 0.1	≤0.05	0.1	0.1
Bacteroides fragilis	PZFX	1.56 - >100	6.25	6.25	25
	CAZ	6.25 - >100	25	>100	>100
	IPM	≤0.05 - 12.5	0.2	0.39	0.78
	GM	>100 - >100	>100	>100	>100
	CPFX	1.56 - >100	6.25	25	50
Prevotella spp.	PZFX	0.39 - >100	1.56	6.25	50
	CAZ	≤0.05 - >100	1.56	100	>100
	IPM	≤0.05 - 25	≤0.05	0.1	0.2
	GM	25 - >100	>100	>100	>100
	CPFX	0.39 - >100	1.56	12.5	50
Mycobacterium tuberculosis	PZFX	1 - 8	4	-	4
	CPFX	0.125 - 2	0.5	-	1
	SPFX	≤0.063 - 1	0.125	-	0.25
	RIF	≤0.063 - 1	≤0.063	-	0.25
Mycobacterium avium	PZFX	2 - >128	16	-	64
	CPFX	0.25 - 32	2	-	8
	SPFX	0.125 - 16	2	-	8
	RIF	4 - >128	64	-	128
Mycobacterium intracellulare	PZFX	2 - 128	4	-	16
	CPFX	0.25 - 16	1	-	16
	SPFX	0.5 - 16	1	-	8
	RIF	0.125 - 128	1	-	32
Mycopalsma pneumoniae	PZFX	4 - 8	8	-	8
	CPFX	0.5 - 2	1	-	1
	SPFX	0.0625 - 0.125	0.125	-	0.125
	EM	0.0039 - 0.156	0.0156	-	0.0156

*Inoculam size : 10*CFU/ml. PZFX: pazufloxacin, CAZ:ceftazidime, IPM: imipenam, GM: gentamicin, CPFX: ciprofloxacin, SPFX: sparfloxacin, RIF:rifampicin, EM: erythromycin

CLINICAL ROLE OF PZFX

New-quinolone antibacterial drugs have broader antibacterial spectrum as compared to the knownb-lactam group antibacterial drugs and bactericidal effect occurs in short time due to which their empiricuse for patients suffering from such severe and intractable infections is possible. PZFX easily exhibits bactericidal characteristic within body that is possessed by such new-quinolon eantibacterial drugs and furthermore, blood concentration higher than the existing new-quinolone antibacterial drugs is obtained. Therefore, we think its empiric use as broad spectrum antibacterial drug similar to injectable b-lactam group antibacterial drugs are possible[9]. Actually, satisfactory treatment results were obtained in cases that did not respond to other drugs as given in the collected clinical test results and moreover, clinical effect same as known broad spectrum injectable cephem group antibacterial drugs was confirmed in comparative tests. However, direct evidence that reflects strong concentration-dependence bactericidal ability in short period that is the characteristic of new-quinolone antibacterial drugs, which was not seen in b-lactam group antibacterial drugs, was not obtained. On the other hand, regarding safety, number of cases was limited in the treatment trials conducted at the time of development however results not inferior to

injectable β-lactam group antibacterial drugs, reflecting results of basic study were obtained.
In conclusion, PZFX is anticipated to become treatment drug against severe and intractable infections that do not respond to other drugs**.** Moreover, it can be anticipated that such use will lower the risk of appearance of resistant bacteria caused due to use biased to b-lactam group. As explained above, PZFX is judged to be an injectable new-quinolone group antibacterial drug that can be used safely similar to the known injectable antibacterial drugs, from the results of clinical test and new clinical role as newquinolone group injectable broad spectrum antibacterial drug is anticipated[10].
As the current clinical role, it is predicted that penicillin group or first and second generation cephem group drugs are ineffective or not appropriate while collecting the actual results regarding safety at clinics hereafter. Use of third generation cephem group or carbapenem group drugs in infections is recommended and moreover, it can also be called as substitute drug similar to third generation cephem group or carbapenem group drugs.

CONCLUSION

PZFX is an injectable new-quinolone antibacterial drugs that was first produced in Japan, from which excellent clinical effect is anticipated since blood concentration higher than known oral new-quinolone antibacterial drugs is obtained. At the same time, the fact that it can be used safely was confirmed in clinical test stage including comparative tests with injectable cephem group antibacterial drug CAZ. Moreover, it showed efficacy against cases in which known injectable drugs showed insufficient effect. The role of this drug as a new choice against bacterial infection will become clear by collecting actual data of safety and efficacy at clinics and it is anticipated that it will help suppress appearance of resistant bacteria.

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