PHARMACOKINETIC STUDY OF MOXIFLOXACIN IN CHRONIC PANCREATITIS COMPLICATED WITH PANCREATIC CYSTS

A. V. Ovsyankin[1], A. A. Martinovitch[2], S. A. Gerasimov[1], P. V. Reznik[1]

[1]*Smolensk State Medical Academy, Smolensk, Russia*

[2]*Institute of Antimicrobial Chemotherapy, Smolensk, Russia*

Key words: moxifloxacin, cyst, concentration, pancreatitis, pharmacokinetic

Introduction

Cysts of the pancreas (PC) are late complications of acute or chronic pancreatitis affecting the severity of the patients that increase the length of stay of patients in connection with the possible development of complications and the need for surgical treatment. As a result of chronic pancreatitis PC develops in 20-40% of patients and in acute pancreatitis — in 5.1% of cases. Infected PC, pancreatic abscess and infected pancreatic necrosis — different in severity, course, outcome and treatment strategies late infectious complications of pancreatitis, emerging from the 2-3rd week of illness.

From 15 to 50% of the PC, which developed as a result of acute and chronic pancreatitis are infected. Patients with infected PC usually do not complain, pointing to the septic nature of the disease, while patients with infected necrosis and abscess pancreatogenic are in a serious condition that requires immediate correction. Mortality in patients with infected PC is 6-9%, with pancreatogenic abscesses — 18-25%, and in patients with infected pancreatic necrosis as high as 48%.

Infectious complications of the PC in the structure of all the complications associated with the PC, are the most common, infection can occur spontaneously or as a result of diagnostic procedures. The factors include infection PC invasive methods of diagnosis and treatment, including such widespread manipulation as retrograde cholangiopancreatography and ultrasound-guided puncture with aspiration of the content or subsequent drainage, and in some cases there is superinfected PC.

According to the literature, microbiological picture of all kinds of infectious complications of acute and chronic pancreatitis is quite similar, and consists mainly of gram-negative intestinal microflora, most often — Escherichia coli. However, quite often infected PC are allocated, and other members of the family, such as Enterobacter spp., Klebsiella spp. etc., and Gram (-) and Gram (+) anaerobes, Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa. More than 50% of the PC infected with a mixed flora. In the literature, there are isolated reports of MRSA

isolation from pancreatic abscess, Mycobacterium tuberculosis and the Association of Haemophilus influenzae and Eikenella corrodens.

Infectious complications associated with PC, is a serious problem because of the lack of uniform standards for antimicrobial therapy and prevention, taking into account the pharmacokinetic characteristics used antibiotics. To conduct adequate, combined with surgery, antibiotic treatment of infected PC and prevention of PC infection in surgical interventions not guided by sensitivity dedicated or intended to antibiotics. And of course, with the assigned antimicrobial should create a fabric, and the secret contents PC effective inhibitory concentrations. Imipenem, meropenem and fluoroquinolones (PC) II generation (tsiproloksatsin, ofloxacin), the most frequently used for the prevention of infectious complications in the treatment of acute pancreatitis, have some of the highest rates of penetration into the tissue of the pancreas. In general, carbapenems potentially cover the entire range of the most probable pathogens PC FC but there are such advantages as lower cost and the possibility of oral intake. However, early FH significantly lower than the breadth of the spectrum of activity against a range of potential pathogens (Gram-positive and anaerobic flora) IV-generation fluoroquinolones (moxifloxacin). Furthermore, moxifloxacin (MOX) has a multiplicity of convenient dosing, moreover, there is evidence of a good penetration of the drug into the tissue of the pancreas of animals and humans. As for pharmakokineteks MOX in the PC, in literature, such data are not present.

The aim of research is concentration of MOX assessment after a single intravenous injection of blood plasma and contents of the PC in patients with chronic pancreatitis (CP), obtained through an operation or invasive diagnostic procedures.

Materials and methods

The study included 27 patients with chronic pancreatitis complicated by the PC, which are obtained from 28 samples of the contents of cysts and 27 plasma samples. The clinical material was obtained three hours after a single intravenous injection of 400 mg of the original drug MOX. Blood collection was carried out from a vein. PC aspirate contents obtained by percutaneous puncture under ultrasound (10 patients) during the operation of internal drainage (11 patients) and plasma scalpel surgery cystectomy (6 patients).

Concentration of MOX established by reversed-phase high-performance liquid chromatography. For the separation of analytes used chromatographic column Symmetry C18 (3,9 × 150 mm) and mobile phase consisting of 15% acetonitrile, 85% 50 mM ammonium chloride, 7 mM tetrabutylammonium hydroxide (pH 3,0 with citric acid). There was used isocratic with a flow rate of 1 ml/min. Fluorescence detection was carried out with activation at 287 nm and emission at 465

nm, was used as an internal standard gemifloxacin. Clinical samples were prepared by diluting the plasma or liquid PC equal amount of acetonitrile, the supernatant obtained after centrifugation was bred double volume of water.

The reliability of the method was confirmed by the addition of quality controls for determination of the accuracy and precision of sample preparation with an accuracy of 3%. For each independently prepared two sets of quality control at a concentration of moxifloxacin 4 ug/ml (SQC1) and 0.125 mg/ml (SQC2). They were included in the analysis in a random order, along with calibrators and prototypes. For SQC1 30 l stock solution was added to moxifloxacin 970 l water, 10 l of the resultant solution was added to 110 l of "clean" plasma. For SQC2 1 microliter stock solution of moxifloxacin added 1000 l of water, 10 ul of the resulting solution was added to 110 l of "clean" plasma. Then 89 l stock solution was added to 910 gemifloxacin mu.l of water, 10 ul of this solution was added to each quality control (final concentration gemifloxacin — 11 ug/ml). The resulting samples were subjected to sample preparation. Indicated values are compared with theoretical concentrations (Table 1).

Table 1

Measured concentration of MOX in prepared quality-controls

Day	Measured concentration mg/mL	
	control 1	control 2
1st	4,135	0,140
2nd	4,091	0,144
Theoretical concentration	4,036	0,134
Max. deviation, %	2,453	7,138

To determine the concentration of moxifloxacin in the samples used in a series of 6 gauge the levels obtained by the double dilution. For their preparation 55 l analytical standard stock solution were diluted in 945 l water. 10 ul of this solution was added to the tube with 210 ul of plasma was stirred (calibration level 1). 110 l of the obtained calibration level is transferred to the next tube with 110 ul plasma (Calibration Level 2), etc. to 6th tube. From the last tube 110 l of the solution were removed. To account for the loss of moxifloxacin as a result of binding to plasma proteins and deposition during sample preparation in each calibration level was added internal standard of quality — gemifloxacin. It was obtained by diluting 89 l of an analytical standard stock solution of 910 l of water. 10 ul of this solution was added to each calibration level. The resulting samples were subjected to sample preparation. The calculation was made in proportion to the loss of

moxifloxacin loss of internal standard Thus, the calibration levels were obtained with known concentrations of moxifloxacin and gemifloxacin (Table 2). Calibration was linear in the concentration range of 0,125-4 mg/L, with a correlation coefficient ≥0,9998.

Table 2

The concentration of analytical standards to gauge levels

Calibrators	The concentration of moxifloxacin, mcg/ml	The concentration of gemifloxacin, mcg/ml
Level 1	4	11
Level 2	2	11
Level 3	1	11
Level 4	0,5	11
Level 5	0,25	11
Level 6	0,125	11

Results and discussion

To calculate the concentration of moxifloxacin was used unweighted linear regression to the area of chromatographic peaks with respect to the theoretical concentration of moxifloxacin in gauge levels. All calculations were performed using the software Millennium v2.1. Analysis of the calibration standards was carried out daily for each group of samples. Deviation obtained from the theoretical concentration (%) was recorded for all calibration points (Table 3).

Table 3

Linear regression and the percentage differences for individual calibration points used to estimate the concentration of MOX

Day	Linear Regression Indicators *			The true concentration of moxifloxacin (in mcg/mL) /% deviation of calibration points from the theoretical concentration					
	R^2	*Slope*	*Intercept*	level1	level2	level 3	level4	level 5	level 6
1-й	0,999637	1,959287	–0,021912	3,990	2,011	1,004	0,488	0,255	0,124
2-й	0,998796	1,946248	–0,015045	4,011	2,067	0,996	0,493	0,239	0,128
Theoretical concentration				4,036	2,018	1,009	0,505	0,252	0,126
Max. deviation, %				1,145	2,423	1,288	3,366	5,159	1,587

Note. * Linear regression equation: response detektoraSlope × conc. (pg/ml) + Intercept; R2 — coefficient of determination.

The concentration of MOX contents PC CP patients was 0,04-1,98 mg/l (mean ± SD0, 57 ± 0,41) (Table 4). Suitable concentrations in plasma MOX were 0,86-2,45 mg/l (mean ± SD1, 67 ±

0,39. Concentration moxifloxacin contents PC 3 hours after intravenous administration of 400 mg of the drug was generally lower than that in the blood plasma, but above the minimum inhibitory concentration (MIC) for most bacterial pathogens, established by the European Committee for determination of sensitivity to antibiotics (EUCAST) When the contents of the culture study PC growth of pathogenic organisms have been identified. Furthermore, all operated patients treated MOX no signs of infectious complications in the postoperative period.

Table 4

The concentrations of moxifloxacin in biological samples

Moxifloxacin		Moxifloxacin	
Samples	mcg/ml	Samples	Mcg/ml
Moxi_1a	0,618	Moxi_14b	2,019
Moxi_1b	1,478	Moxi_15a	0,299
Moxi_2a	0,625	Moxi_15b	1,718
Moxi_2b	1,985	Moxi_16a	0,286
Moxi_3a	0,594	Moxi_16b	1,297
Moxi_3b	1,491	Moxi_17a	0,417
Moxi_4a	0,718	Moxi_17b	1,704
Moxi_4a	1,3	Moxi_18a	0,548
Moxi_4b	0,339	Moxi_18b	0,864
Moxi_5a	0,17	Moxi_19a	0,489
Moxi_5b	1,488	Moxi_19b	2,448
Moxi_6a	0,265	Moxi_20a	1,981
Moxi_6b	1,536	Moxi_20b	1,783
Moxi_7a	0,339	Moxi_21a	0,517
Moxi_7b	0,86	Moxi_21b	1,799
Moxi_8a	0,483	Moxi_22a	0,692
Moxi_8b	1,508	Moxi_22b	1,102
Moxi_9a	0,163	Moxi_23a	0,036
Moxi_9b	0,878	Moxi_23b	2,025
Moxi_10a	0,381	Moxi_24a	0,979
Moxi_10b	1,831	Moxi_24b	2,189
Moxi_11a	0,714	Moxi_25a	1,146
Moxi_11b	1,583	Moxi_25b	1,417
Moxi_12a	0,549	Moxi_26a	1,086
Moxi_12b	2,444	Moxi_26b	1,67
Moxi_13a	0,127	Moxi_27a	0,082
Moxi_13b	1,634	Moxi_27b	1,807

Moxi_14a	0,726		

Note. «a» — The result of research concentration of MOX in the aspirate PC, «b» — the result of research concentration of MOX in the PC.

Given the fact that the concentration of MOX contents PC higher than the MIC for the majority of infectious complications associated with the PC, MOX could potentially be effective during the perioperative prophylaxis and therapy in patients with chronic pancreatitis complicated by a cyst. Moreover, in contrast to ofloxacin and ciprofloxacin introduction of MOX does not need to be combined with the introduction of metronidazole, as the drug has its own distinct anti-anaerobic effect.

References

1. Antibiotic prophylaxis in severe acute pancreatitis/H. G. Berger, B. Rau, R. Isenmann [et al.] // Pancreatol. — 2005. — Vol. 5. — P. 10–19.
2. Banks P. A. Practice guidelines in acute pancreatitis/P. A. Banks, M. L. Freeman // Am. J. Gastroenterol. — 2006. — Vol. 101. — P. 2379–2400.
3. Baron T. H. Acute necrotizing pancreatitis/T. H. Baron, D. E. Morgan // N. Eng. J. Med. — 1999. — Vol. 340. — P. 1412–1417.
4. Borman P. C. Chronic pancreatitis/P. C. Borman, I. J. Beckingham // Br. Med. J. — 2001. — Vol. 322. — P. 660–663.
5. Dunkin B. J. Ultrasound-direct percutaneous endoscopic cyst-gastrostomy for the treatment of a pancreatic pseudocyst/B. J. Dunkin, J. L. Ponsky, J. C. Hale // Surg. Endosc. — 1998. — Vol. 12. — P. 1426–1429.
6. Frommeyer L. Iatrogenic Candida infection in pancreatic pseudocyst/L. Frommeyer, P. Bihl, H. A. Schmidt-Wilcke // Gastroenterol. — 1991. — Vol. 29. — P. 392–394.
7. Gopal Rao G. Linesolid levels in pancreatic abscess/G. Gopal Rao, A. Steiger // Clin. Microbiol. Infect. — 2001. — Vol. 7. — P. 269.
8. Human pancreatic tissue concentration of bactericidal antibiotics/M. Büchler, P. Malfertheiner, H. Friess [et al.] // Gastroenterol. — 1992. — Vol. 103. — P. 1902–1908.
9. Internal drainage of infected pancreatic pseudocysts: safe or sorry?/D. Boerman, T. M. Van Gulic, H. Obertop, D. J. Gouma // Dig. Surg. — 1999. — Vol. 16. — P. 501–505.
10. Isenmann R. Natural history of acute pancreatitis and the role of infection/R. Isenmann, H. G. Berger // Bailliere's best practice & research. — 1999. — Vol. 13. — P. 291–301.
11. Kolvenbach H. Infected pancreatic necrosis possibly due to combined percutaneous aspiration, cystogastric pseudocyst drainage and injection of a sclerosant/H. Kolvenbach, A. Hirner // Endosc. — 1991. — Vol. 2. — P. 102–105.
12. Ljubicic N. Inflamed pancreatic pseudocysts: optimization of pseudocysts fluid culture technique/N. Ljubicic, A. Bilic // Zeitschrift für Gastroenterologie. — 1993. — Vol. 3. — P. 198–200.
13. Long term results of percutaneous catheter drainage of pancreatic pseudocysts/E. Criano, A. A. De Stefano, T. M. Weiner, P. F. Jaques // Surg. Gynecol. Obstetrics. — 1992. — Vol. 4. — P. 293–298.
14. Lumsden A. Secondary pancreatic infection/A. Lumsden, E. L. Bradley // Surg. Gynecol. Obstetrics. — 1990. — Vol. 170. — P. 459–467.

15. Lutwick L. I. Pancreatic abscess with Haemophilus influenzae and Eikenella corrodens // J. Am. Medical Association. — 1976. — Vol. 236. — P. 2091–2092.
16. Mandell G. L. Principles and practice of infectious diseases/G. L. Mandell, J. E. Bennett, R. Dolin. — 7th ed. — Philadelphia : Elsevier Churchill Livingstone, 2010.
17. Natural course of acute pancreatitis/H. G. Berger, B. Rau, J. Mayer, U. Pralle // World J. Surg. — 1997. — Vol. 21. — P. 130–135.
18. O'Malley V. P. Pancreatic pseudocysts: cause, therapy, and results/V. P. O'Malley, J. P. Cannon, R. G. Postier // Am. J. Surg. — 1985. — Vol. 150. — P. 680–682.
19. Pancreatic concentration of cefepime/R. Delcenserie, M. P. Dellion-Lozinguez, T. Yzet [et.al.] // J. Antimicrob. Chemother. — 2001. — Vol. 47. — P. 711–713.
20. Pancreatic fluid collections: diagnostic and therapeutic implications of percutaneous drainage guided by ultrasound/E. Malecka-Panas, A. Juszynski, J. Chrzastek [et al.] // Hepato-Gastroenterol. — 1998. — Vol. 45. — P. 873–878.
21. Pancreatic infection in severe pancreatitis: the role of fungus and multiresistant organisms/B. Gloor, C. A. Müller, M. Worni [et al.] // Arch. Surg. — 2001. — Vol. 136. — P. 592–596.
22. Pancreatic abscesses/P. Kothaj, P. Melus, L. Marco, A. Pelikan // Bratislavske Lekarske Listy. — 1995. — Vol. 96. — P. 250–253.
23. Penetration of moxifloxacin into the human pancreas following a single intravenous or oral dose/R. Wacke, S. Forster, U. Adam [et al.] // J. Antimicrob. Chemother. — 2006. — Vol. 58. — P. 994–999.
24. Percutaneous drainage of infected pancreatic pseudocysts/S. G. Gerzof, W. C. Johnson, A. H. Robbins [et al.] // Arch. Surg. — 1984. — Vol. 119. — P. 888–893.
25. Percutaneous drainage of infected and noninfected pancreatic pseudocysts: experience in 101 cases/E. VanSonnenberg, G. R. Wittich, G. Casola [et al.] // Radiol. — 1989. — Vol. 170. — P. 757–761.
26. Pharmacokinetics of the 8-methoxyquinolone, moxifloxacin: tissue distribution in male rats/H. M. Siefert, C. Kohlsdorfer, W. Steinke [et al.] // J. Antimicrob. Chemother. — 1999. — Vol. 43. — P. 61–67.
27. Pseudocysts in acute nonalcoholic pancreatitis — incidence and natural history/A. Maringhini, R. Uomo, R. Patti [et al.] // Dig. Dis. Sci. — 1999. — Vol. 44. — P. 1669–1673.
28. Radiology of pancreatic tuberculosis: a report of three cases/D. Takhtani, S. Gupta, K. Suman [et al.] // Am. J. Gastroenterol. — 1996. — Vol. 9. — P. 1832–1834.

29. Secondary pancreatic infections: are they distinct clinical entities?/I. J. Fedorac, T. C. Ko, G. Djuricin [et al.] // Surg. — 1992. — Vol. 112. — P. 824–830.
30. Singer M. V. Non-surgical therapy of pancreatitis complications (pseudocyst, abscesses, stenoses)/M. V. Singer, K. Forssmann // Schweizerische Rundschau Fur Medizin Praxis. — 1994. — Vol. 83. — P. 865–869.
31. The penetration of ciprofloxacin into human pancreatic and peripancreatic necroses in acute necrotizing pancreatitis/U. Adam, S. Herms, U. Werner [et al.] // Infection. — 2001. — Vol. 29. — P. 326–331.
32. The penetration of moxifloxacin into the pancreas of male rats in experimental acute necrotizing pancreatitis/R. Wacke, S. Park, R. G. Mundkowski [et al.] // Chemother. — 2003. — Vol. 49. — P. 167–171.
33. The therapy of acute pancreatitis. General guidelines/M. Runzi, P. Layer, M. W. Buchler [et al.] // Zeitschrift fur Gastroenterologie. — 2000. — Vol. 38. — P. 571–581.
34. Trinidad E. E. Pancreatic abscess and infected pseudocyst/E. E. Trinidad, C. H. Ramirez-Ronda // Boletin de la Asociación Médica de Puerto Rico. — 1994. — Vol. 86. — P. 68–70.
35. Uhl W. Infections complicating pancreatitis: diagnosing, treating, preventing/W. Uhl, R. Isenmann, M. W. Buchler // New horizons (Baltimore, Md). — 1998. — Vol. 6. — P. 72–79.
36. Yung-Fang C. Abdominal fluid collection secondary to acute pancreatitis: treated with percutaneous catheter drainage/C. Yung-Fang, C. Hsein-Jar, C. Jeng-Her // Chin. Med. J. — 1997. — Vol. 60. — P. 265–272.

Pharmacokinetic study of moxifloxacin in chronic pancreatitis complicated with pancreatic cysts

A. V. Ovsyankin[1], A. A. Martinovitch[2], S. A. Gerasimov[1], P. V. Reznik[1]

[1]*Smolensk State Medical Academy, Smolensk, Russia*

[2]*Institute of Antimicrobial Chemotherapy, Smolensk, Russia*

Key words: moxifloxacin, cyst, concentration, pancreatitis, pharmacokinetic

Infectious complications of pancreatic cysts (PC) is one of the problem of modern medicine due to insufficient data on pharmacokinetic of majority of antimicrobials resulting to the lack of standards for antimicrobial therapy and prophylaxis of this disorder. One of the promising options for the treatment and prophylaxis of PC-associated infections is moxifloxacin, but there is no data available on its pharmacokinetic in PC. Twenty eight PK samples and 27 serum samples from 27 patients with PK cysts were included in the study. Samples were obtained 3 hours after 400 mg IV dose of moxifloxacin. Drug concentrations were measured using reversed-phase high performance liquid chromatography. All calculations were done using Millennium v2.1 software. Moxifloxacin concentrations in PCs were 0.04–1.98 mg/l (mean±SD 0.57±0.41). Corresponding serum concentrations were 0.86–2.45 mg/l (mean±SD 1.67±0.39). In general, PC concentrations of moxifloxacin were lower than serum concentrations, but still higher than indexes of minimal inhibiting concentration for majority of bacterial pathogens. Moreover, no bacterial growth was detected in all PC samples and no clinical signs of infections were registered. Thus, it can be concluded that moxifloxacin may be an interesting option for the therapy and prophylaxis of PC-associated infections.