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RAPID COMMUNICATION

In vitro activity of moxifloxacin and piperacillin/sulbactam against pathogens of acute cholangitis

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Abstract

AIM: To analyze the *in vitro* activity of moxifloxacin and piperacillin/sulbactam against pathogens isolated from patients with acute cholangitis.

METHODS: In this prospective study a total of 65 patients with acute cholangitis due to biliary stone obstruction (n = 7), benign biliary stricture (n = 16), and malignant biliary stricture (n = 42) were investigated with regard to spectrum of bacterial infection and antibiotic resistance. Pathogens were isolated from bile cultures in all study patients. In 22 febrile patients, blood cultures were also obtained. *In vitro* activity of moxifloxacin and piperacillin/sulbactam was determined by agar diffusion.

RESULTS: Thirty-one out of 65 patients had positive bile and/or blood cultures. In 31 patients, 63 isolates with 17 different species were identified. The predominant strains were *Enterococcus species* (26/63), *E.coli* (13/63) and *Klebsiella species* (8/63). A comparable *in vitro* activity of moxifloxacin and piperacillin/sulbactam was observed for *E.coli* and *Klebsiella species*. In contrast, *Enterococcus species* had higher resistances towards moxifloxacin. Overall bacteria showed antibiotic resistances *in vitro* of 34.9% for piperacillin/sulbactam and 36.5% for moxifloxacin.

CONCLUSION: *Enterococcus species*, *E.coli* and *Klebsiella species* were the most common bacteria isolated from bile and/or blood from patients with acute cholangitis. Overall, a mixed infection with several species was observed, and bacteria showed a comparable *in vitro* activity for piperacillin/sulbactam and moxifloxacin.

Key words: Cholangitis; Acute cholangitis; Endoscopy; Antibiotics; Moxifloxacin; Piperacillin; Sulbactam; Biliary stricture; Resistance; Bacterial pathogens

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INTRODUCTION

Acute cholangitis, first described by Charcot in 1877 is a frequent and potentially serious complication in patients with bile duct obstruction. Ductal obstruction leads to a raised intrabiliary pressure with cholangiovenous reflux and bacteremia, which may progress to septicaemia[1]. Ductal stones, benign or malignant biliary strictures are reasons for the obstruction. Biliary decompression by endoscopic or percutaneous transhepatic procedures and selection of appropriate antibiotics are crucial in the therapy of these patients[2-5]. The efficacy of antibiotics in the treatment of biliary infections depends on the microbiological activity against the most common pathogens and the excretion of the antibacterial agents in the obstructed biliary tract. In case of complete obstruction of the common bile duct, no significant biliary excretion of the antibiotics occurs, so that biliary

bactericidal concentrations cannot be achieved[6,7]. However, recently a sufficient biliary concentration of the fluoroquinolone moxifloxacin in patients with obstructive cholangitis was reported[8]. Because bacteremia may progress to septicaemia, a high level of serum concentrations of the antibiotic agents is also important for the treatment of biliary tract infections. Although acute cholangitis is a common clinical problem associated with a high level of morbidity and mortality, there is no standardized approach for therapy of this disease. The selection of antibacterial agents is based on the severity of the disease, the expected biliary pathogens or the activity of antibacterial agents against the isolated bacteria from blood or bile cultures. Broad spectrum antibiotics, active against gram negative and gram positive organisms, are the preferred treatment[2,9-11]. Therefore, in case of severe cholangitis, the mostly preferred drug is piperacillin, a broad spectrum penicillin. In a prospective randomised trial including patients with acute cholangitis, equal clinical efficacy was observed with piperacillin alone compared to ampicillin plus tobramycin[12]. The combination of piperacillin with the β-lactamase inhibitor sulbactam might be an alternative procedure when the resistance pattern shows a relatively high incidence of ureidopenicillin-resistant *E.coli* or *Klebsiella species*[13]. Because of increasing resistance and allergic reactions against penicillin, other antibacterial agents for the treatment of acute cholangitis become necessary. Moxifloxacin is characterized by an enhanced activity against gram positive, gram negative and in anaerobic organisms and by a sufficient concentration in the obstructive bile duct. Therefore it may be an alternative antibacterial treatment in patients with acute cholangitis. To address this question, we performed a prospective trial to analyze the *in vitro* activity of moxifloxacin and piperacillin/sulbactam against pathogens isolated from patients with acute cholangitis.

MATERIALS AND METHODS

Study population

The study included 65 consecutive patients suffering from acute cholangitis who were treated between February 2004 and November 2005 in the Department of Gastroenterology at the Technical University of Munich. All of the following criteria had to be fulfilled: (1) clinical diagnosis of acute cholangitis, (2) elevated cholestasis parameter (bilirubin > 3 mg/dL), (3) elevated infection parameters (leucocytes > 12 G/L, c-reactive protein > 3 mg/dL) or fever (> 38.5℃), and (4) age 18-90 years. Exclusion criteria were as follows: (1) primary sclerosing cholangitis, (2) liver cirrhosis, (3) liver transplantation, (4) acquired immunodeficiency syndrome (AIDS), (5) primary immunodeficiency syndrome, (6) therapy with glucocorticoids and other immunosuppressant drugs, (7) leucopenia (leucocytes < 1 G/L), and (8) infection focus other than acute cholangitis.

Isolation of bacteria

From all patients included in this study, bile samples for culture were taken. Bile was obtained by endoscopic retrograde cholangiography (ERC) or by percutaneous transhepatic biliary drainage (PTBD). ERC and biliary drainage were performed with a standard videoduodenoscope OlympusTFJ 160-R. Endoscopic sphincterotomy (EST) was conducted using an Olympus papillotome introduced over a Terumo guide wire. At ERC, intraductal bile was collected before contrast agent injection by passing a sterile standard ERC catheter into the obstructed bile duct and aspirating bile into a sterile 10 mL syringe. In case of PTBD, 2-4 mL bile was collected into a sterile 10 mL syringe after penetration of the bile duct with the puncture needle. Thereafter, a percutaneous transhepatic biliary catheter was inserted by the Seldinger technique. Because of the percutaneous placement of this catheter, bile could be obtained all the time in case of fever, chills and increasing infection parameters (leucocytes, c-reactive protein). In 22 febrile patients (temperature > 38.5℃), blood cultures were also obtained. Typically, 10 mL of blood was obtained and transferred into aerobic and anaerobic culture broth (BacTec system, Becton Dickinson, Heidelberg, Germany).

Microbiological investigation

In case of positive blood- and/or bile cultures, the *in vitro* activity of moxifloxacin and piperacillin/sulbactam was performed by agar diffusion assay test.

The bile/specimen sampled was examined for aerobic and anaerobic bacteria. In each case, 50-100 μL bile/specimen were both transferred into liquid nutrient media (glucose broth, thioglycollate broth) and spread on solid culture media (Columbia sheep blood agar, chocolate agar, McConkey agar, Schädler anaerobic agar, Schädler KV anaerobic agar, and Sabouroud agar). Subsequently, the culture media were incubated at 37℃. The aerobic cultures were incubated for 48 h, with the first readout taken after 24 h. The anaerobic cultures were monitored for the first time after 48 h and processed further as required. To identify bacteria in the blood, one aerobic and one anaerobic blood culture bottle (BacTec system, Becton Dickinson, Heidelberg, Germany) were each inoculated with 10 mL of venous blood. The blood cultures were incubated at 37℃ for 5 d. For control purposes and to exclude failure of automatic detection of the BacTec system each flask was subcultivated under aerobic (chocolate agar in 10% CO_2) and anaerobic conditions (Schädler anaerobic agar) at the end of the incubation period. Cultivable germs were identified using the ATB, API or VITEK system (BioMérieux, Nürtingen, Germany). In order to identify antimicrobial inhibitors approximately 10 μL of fluid specimen were placed in the depression of an agar plate containing a suspension of spore forming bacteria. With an antibiotic being present and taking effect in the specimen a clear inhibition zone was to be seen around the point of application. Colony forming units were

Table 1 Patient characteristics, physical and laboratory parameters on admission

		Standard values	Scale unit
Number of patients	65	-	-
Mean age	68 ± 12.3	-	-
Gender			
Male	32	-	-
Female	33	-	-
Bilirubin	7.9 ± 7.4	< 1.2	mg/dL
Alkaline phosphatase	675 ± 510	40-120	U/L
γ-Glutamyltransferase	697 ± 682	< 66	U/L
Aspartate aminotransferase	193 ± 300	10-50	U/L
Alanine aminotransferase	136 ± 147	10-50	U/L
Leucocytes	16.9 ± 10.7	4-9	G/L
C-reactive protein	17.3 ± 9.5	< 0.5	mg/dL

not determined in this study. Antibiotic susceptibility testing was performed using both the disk diffusion test or the MIC test using the VITEK system (BioMérieux, Nürtingen, Germany) or the Etest system (AB Biodisk, Solna, Sweden) according to the recommendations of the CLSI (Clinical Laboratory Standards Institute; formerly NCCLS/National Committee for Clinical Laboratory Standards).

RESULTS

During the study period from February 2004 to November 2005, a total of 65 consecutive patients with acute cholangitis were included in the current clinical trial. The patients had the following characteristics: mean age 68 ± 12.3 years, 32 male and 33 female, bilirubin 7.9 ± 7.4 mg/dL, alkaline phosphatase 675 ± 510 U/L, γ-glutamyltransferase 697 ± 682 U/L, aspartate aminotransferase 193 ± 300 U/L, alanine aminotransferase 136 ± 147 U/L, leucocytes 16.9 ± 10.7 G/L, c-reactive protein 17.3 ± 9.5 mg/dL (Table 1).

Obstruction of the bile duct was caused by gallstones in 7/65 (10.8%) patients, benign strictures in 16/65 (24.6%) patients and malignant strictures of the biliary tract in 42/65 (64.6%) patients.

Thirty-one out of 65 patients had positive bile- and/or blood cultures. Sixty-three bacterial isolates and 17 different bacterial species were identified from 31 patients. The predominant isolated bacteria were *Enterococcus species* (26/63), *E.coli* (13/63), and *Klebsiella species* (8/63). Thereby, three quarter (74.6%) of the isolated bacteria were obtained from these predominant species, while the remaining quarter (25.4%) consisted of 7 different types. Within the group infected with *Enterococcus species*, *Enterococcus faecium* and *Enterococcus faecalis* were most frequent with 8 and 7 isolates, respectively. Bacteriobilia was documented in 22/65 patients and was polymicrobial in 17 patients (77.3%). Positive blood culture were obtained in 13/65 patients and was polymicrobial in only 1 patient (7.7%).

The resistance pattern of the isolated pathogens was investigated by an *in vitro* activity assay. Table 2 gives an overview of all bacterial pathogens and their resistance patterns regarding moxifloxacin and piperacillin/sulbactam. In summary, 34.9% (22/63) of all isolated pathogens were resistant, 6.4% (4/63) were intermediately resistant, and 58.7% (37/63) were susceptible to piperacillin/sulbactam. In comparison to these results 36.5 % (23/63) of all isolated pathogens were resistant, 9.5% (6/63) intermediate resistance, and 54% (34/63) susceptible to moxifloxacin (Figure 1).

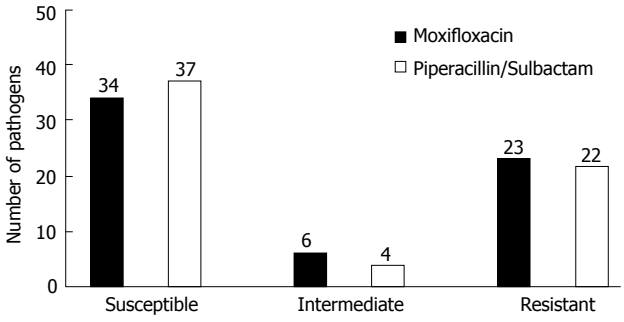

Figure 1 Comparison of *in vitro* activity of moxifloxacin and piperacillin/sulbactam in all isolated bacterial pathogens.

DISCUSSION

Acute cholangitis is an infection of the obstructed biliary tract with a wide spectrum of pathogens. Common microbial populations associated with cholangitis include gram-negative bacteria like *E.coli* and *Klebsiella species*. Gram-positive organisms, mainly *Enterococcus species* and anaerobes, are also found[14-21]. While previous works found *E.coli* infection in 20.9% and *Enterococcus species* in 20.9%[17], our current results reveal that the most common isolates are *Enterococcus species* [41.3% (26/63)], *E.coli* [20.6% (13/63)] and *Klebsiella species* [12.7% (8/63)]. In addition to this a lot of other bacterial pathogens were isolated by blood and/or bile cultures (Table 2). Thus, the shift towards the higher rate of *Enterococcus species* and the high prevalence of *Klebsiella* infections might be related to the use of wide-spectrum antibiotics used in the past years.

Establishment of biliary drainage is the mainstay of therapy for patients with acute cholangitis. Endoscopic sphincterotomy with subsequent biliary drainage is the therapy of choice, but in case of therapy failure percutaneous transhepatic bile drainage is an alternative method for biliary drainage[22-24]. Nevertheless, once endoscopic and/or percutaneous transhepatic procedures have been performed, the spectrum of bacterial infection might change, and increased frequency of mixed infections has been reported[17]. Our current data are in line with this observation and reveal polymicrobial infections of the biliary tract in 17 out of 22 patients.

Overall, our results indicate that bacterial pathogens could only be isolated in 48% of the patients. Antibiotic treatment has to start early during the infectious process. In clinical practice, it is not possible to isolate bacterial pathogens in all patients and the time to receive the resistance pattern creates a delay of several days. Therefore, knowledge of bacterial spectrum and resistance pattern of antimicrobial agents are essential for the treatment of patients suffering from acute cholangitis.

Table 2 Resistance pattern for moxifloxacin and piperacillin/sulbactam in all pathogens

Pathogens	Moxifloxacin			Piperacillin/Sulbactam		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Enterococcus species	9	4	13	16	1	9
Enterococcus NS	2	4	2	7		1
Enterococcus faecium	1		7	2	1	5
Enterococcus faecalis	4		3	5		2
Enterococcus casseliflavus	2			2		
Enterococcus gallinarum			1			1
Escherichia coli	8	1	4	11		2
Klebsiella species	5	1	2	4	1	3
Klebsiella pneumoniae	3	1	2	2	1	3
Klebsiella oxytoca	2			2		
Enterobacter species	5			3		2
Enterobacter cloacae	3			3		
Enterobacter NS	2					2
Pseudomonas aeruginosa	2		1		1	2
Aeromonas species	1		1			2
Aeromonas hydrophila/caviae	1					1
Aeromonas NS			1			1
Citrobacter freundii	2			1	1	
Coagulase neg. Staphylococcus			2			2
Gram negative rod NS	1			1		
Streptococcus anginosus	1			1		

NS: Not specified.

Finally, it has to be mentioned that in patients with an obstructed biliary tract, the biliary excretion of several antibiotic agents is limited[6,25]. Recently, it was reported that moxifloxacin, a fluoroquinolone, can reach clinically significant concentrations in obstructed biliary tract[8]. Therefore it may be a superior treatment in patients with acute cholangitis that suffer from biliary obstruction. Until now, no data about antimicrobial activity of moxifloxacin against pathogens of acute cholangitis exists. Therefore, we isolated pathogens from patients with acute cholangitis and analyzed the *in vitro* activity of moxifloxacin and piperacillin/sulbactam. Our data show a comparable *in vitro* activity of moxifloxacin and piperacillin/sulbactam in patients with acute cholangitis. Kiesslich *et al*[26] reported a resistance rate of 71.8% (28/39) for piperacillin and 76.7% (33/43) for ampicillin (both without β-lactamase inhibitors) in bacteria isolated from obstructed biliary tract during endoscopic retrograde cholangiography. In this study, the resistance rate for other fluoroquinolones ciprofloxacin and levofloxacin was 19.0% (8/42) and 2.2% (1/45), respectively. In agreement with these results, 96% (122/127) sensitivity to ciprofloxacin and 29% (37/127) sensitivity to ampicillin was reported in other studies[27].

The *in vivo* benefit of fluoroquinolones in patients with biliary tract infections was investigated in several clinical trials. Karachlios *et al*[28] performed a prospective, randomized trial with ofloxacin in one, and ceftriaxone in the other group. The clinical cure or improvement of clinical symptoms was the same in both groups. In another prospective randomized trial, an adequate clinical benefit was shown for ciprofloxacin mono therapy in comparison to a triple therapy with ceftazidime, ampicillin and metronidazole[29]. Also levofloxacin, a newer enantiomer of ofloxacin showed an adequate clinical effect when compared to ceftriaxone[30]. In this prospective randomized trial, patients of both study groups received metronidazole additionally.

Although, moxifloxacin and piperacillin/sulbactam appears to have a comparable *in vitro* activity against pathogens of acute cholangitis, moxifloxacin may have a clinical benefit due to its extensive biliary excretion in obstructed biliary tract. Randomized clinical trials should be performed to evaluate clinical outcome of moxifloxacin in patients with acute cholangitis.

COMMENTS

Background

Cholangitis is a frequent and potentially serious complication in patients with bile duct obstruction. Biliary decompression by endoscopic intervention and selection of appropriate antibiotics are crucial for therapy of these patients. The use of broad-spectrum penicillin is generally accepted. Because of increasing resistance and allergic reactions against penicillin, other antibacterial agents for the treatment of acute cholangitis are essential moxifloxacin is characterized by an enhanced activity against gram-positive and -negative anaerobic organisms as well by a sufficient concentration in the obstructive bile duct. Therefore it may be an alternative antibacterial treatment for acute cholangitis.

Research frontiers

To our knowledge, no study exists investigating the *in vitro* activity of moxifloxacin against pathogens isolated from patients with acute cholangitis. The current study was designed to analyze the *in vitro* activity of moxifloxacin and piperacillin/sulbactam against pathogens of acute cholangitis.

Innovations and breakthroughs

The predominant pathogens isolated from patients with acute cholangitis were *Enterococcus species*, *E.coli* and *Klebsiella species*. A comparable *in vitro* activity of moxifloxacin and piperacillin/sulbactam was observed for *E.coli* and *Klebsiella species*. In contrast, *Enterococcus species* had higher resistances towards moxifloxacin. Overall bacteria showed antibiotic resistances of 34.9% for piperacillin/sulbactam and 36.5% for moxifloxacin.

Applications

These data suggest that moxifloxacin can be used as an alternative antibiotic therapy in patients with cholangitis that show allergic reactions to piperacillin/sulbactam. Additionally, due to the extensive excretion of moxifloxacin in the obstructed biliary tract it may have a clinical advantage compared to the

standard therapy. Randomized controlled trials should be performed to evaluate the clinical outcome of moxifloxacin in patients with acute cholangitis.

Terminology

Acute cholangitis with the triad of jaundice, fever and abdominal pain: was first described by Charcot in 1877. It is a frequent and potentially serious complication in patients with bile duct obstruction due to ductal stones, benign and malignant bile duct strictures. Bile duct obstruction leads to a raised intrabiliary pressure with cholangiovenous reflux and bacteraemia, which may induce sepsis.

Peer review

This manuscript evaluates the relative resistance of bacterial cultures isolated from patients suffering acute cholangitis to piperacillin/sulbactam (the current antibiotic therapy) versus moxifloxacin. It is well designed, performed and written. It is of clinical relevance.

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