In vitro Activity of Sitafloxacin and Other Antibiotics against Bacterial Isolates from HRH Princess Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University and Samitivej Sukhumvit Hospital

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Background: *Sitafloxacin is a newly approved oral fluoroquinolone in Thailand for treatment of respiratory tract and urinary tract infections. Initial in vitro susceptibility testing showed its effect on Escherichia coli with extended-spectrum beta-lactamases (ESBL), Klebsiella pneumoniae with ESBL, Pseudomonas aeruginosa, and carbapenem resistant Acinetobacter baumannii.*
Objective: *To retrospectively review in vitro susceptibility to sitafloxacin on clinical isolates from HRH Princess Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University (SWU) and Samitivej Sukhumvit Hospital (SVH).*
Material and Method: *Between January 2014 and June 2015, all clinical isolates from SWU and SVH that were added to test in vitro susceptibility to sitafloxacin were included in the present study. The susceptibility for sitafloxacin was identified by disk diffusion method with inhibition zone diameter 19 mm or greater, considered to be sensitive, and smaller than 16 mm considered to be resistance. The comparative activities of sitafloxacin to other antibiotics were determined by organisms. All bacteria with count numbers of more than 30 would be shown in results.*
Results: *Among 1,288 clinical isolates from 1,163 clinical specimens that were added in vitro susceptibility test to sitafloxacin, there were 728 clinical isolates from SWU and 560 clinical isolates from SVH. The most common specimens were sputum (482), urine (385), pus (96), and blood (81). Organisms with comparative activities included E. coli, K. pneumoniae, P. aeruginosa, A. baumannii, and Stenotrophomonas maltophilia. The susceptible percentage of sitafloxacin was 72.69% for all E. coli (n = 216) (68.26% for E. coli with ESBL and 86.96% for E. coli without ESBL), 39.31% for all K. pneumoniae (n = 173) (50% for K. pneumoniae with ESBL, 61.11% for K. pneumoniae without ESBL and 13.11% for carbapenem resistant enterobacteriaceae (CRE) strain of K. pneumoniae), 60.66% for P. aeruginosa (n = 366), 66.32% for A. baumannii (n = 386) and 93.94% for S. maltophilia (n = 33). Sitafloxacin had more susceptible percentage as compared to ciprofloxacin for all strains of E. coli, K. pneumoniae, P. aeruginosa, and A. baumannii and more susceptible percentage as compared to levofloxacin for S. maltophilia. Although sitafloxacin might not have good activity against CRE strain of K. pneumoniae, at least some (13.11%) were susceptible as compared to 0% for ciprofloxacin.*
Conclusion: *Sitafloxacin had more susceptible percentage to E. coli, K. pneumoniae, P. aeruginosa, A. baumannii, and S. maltophilia compared to comparative fluoroquinolones. It should be considered an antibiotic for treatment of respiratory tract and urinary tract infections caused by the resistant strains of these bacteria with susceptible proven of in vitro susceptibility.*

Keywords: *Sitafloxacin, Comparative in vitro susceptibility, Fluoroquinolones*

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Sitafloxacin is a new fluoroquinolone approved in Thailand for treatment of urinary and respiratory tracts infections[1,2]. Initial *in vitro* susceptibility testing show its effect on *Escherichia coli* with extended-spectrum beta-lactamases (ESBL), *Klebsiella pneumoniae* with ESBL, *Pseudomonas aeruginosa* and carbapenem resistant *Acinetobacter baumannii*[3-8].

Sitafloxacin is considered for treatment of these bacterial infections in some clinical setting especially in the situation that it has been proven to be *in vitro* susceptible to these bacteria without other

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available oral antibiotics. With these clinical uses, there should be more current data of *in vitro* susceptibility of sitafloxacin for these bacteria. It would be important to understand current activity of sitafloxacin especially in the institution which it was currently used.

Objective

To retrospectively review *in vitro* susceptibility of sitafloxacin on clinical isolates from HRH Princess Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University (SWU) and Samitivej Sukhumvit Hospital (SVH) for determining of its susceptibility to bacterial isolates in comparison with other antibiotics.

Material and Method

Between January 2014 and June 2015, all clinical isolates which were added to test *in vitro* susceptibility to sitafloxacin in both institutions were included in the present study. Clinical isolates that were added to test *in vitro* susceptibility to sitafloxacin were isolates that had potential role of using sitafloxacin such as expecting for multi-drug resistance (MDR) gram negative bacteria as cause of infections or considering effective oral antibiotic for MDR bacterial infections. Clinical isolates with same microbiological sensitivity from a patient would be included only once in one-month period to avoid duplication.

The susceptibility for sitafloxacin was identified by disk diffusion method with inhibition zone diameter 19 mm or greater considered to be sensitive and less than 16 mm considered to be resistance[9,10]. The sitafloxacin disks were manufactured by the Eiken Chemical Co. Ltd., Japan and were generously provided to both institution laboratories by Daiichi Sankyo, Thailand. Both laboratories had approximately a year experience on using sitafloxacin disk diffusion test before initiation of the study. Other antibiotics susceptibility testing would be routinely done by both laboratories.

The activities of sitafloxacin to these organisms were determined by total susceptibility data from both institutions. The comparative activities of sitafloxacin to other antibiotics were determined by organisms. All bacteria with count numbers of more than 30 counts would be shown in results.

The present study was reviewed by SWU Ethic Committee review and was exempted for ethical reviewing. The study was approved by SVH hospital director before SWU Ethic Committee Review. The study was funded by Daiichi Sankyo, Thailand.

Results

One thousand two hundred eighty eight initial isolates were added to the *in vitro* susceptibility test to sitafloxacin between January 2014 and June 2015. There were 728 clinical isolates from SWU and 560 clinical isolates from SVH. All clinical specimens from both institutions were shown in Fig. 1.

The most common specimens were sputum (482), urine (385), pus (96), and blood (81). Sputum was the most common specimen at SWU whereas urine was the most common specimen at SVH.

Twenty-four kinds of organisms were added to test *in vitro* susceptibility to sitafloxacin from SWU and 28 kinds of organisms were added to test *in vitro* susceptibility to sitafloxacin from SVH. Organisms with comparative activities included *E. coli* (n = 216; SVH = 202; SWU = 14), *K. pneumoniae* (n = 173; SVH = 114; SWU = 59), *P. aeruginosa* (n = 366; SVH = 100; SWU = 266), *A. baumannii* (n = 386; SVH = 44; SWU = 342), and *Stenotrophomonas maltophilia* (n = 33; SVH = 30; SWU = 3). The susceptibility of sitafloxacin against these organisms from both institutions was shown in Fig. 2.

Overall *E. coli* were mostly from SVH (202 specimens from 216 specimens). The comparative activity data were only shown for susceptible data (intermediate and resistant results would not be shown). The susceptible percentage of sitafloxacin was 72.69%. Another quinolone that was tested for comparison was ciprofloxacin. The susceptible percentage of ciprofloxacin was 12.04%. The susceptible percentage of other antibiotics included

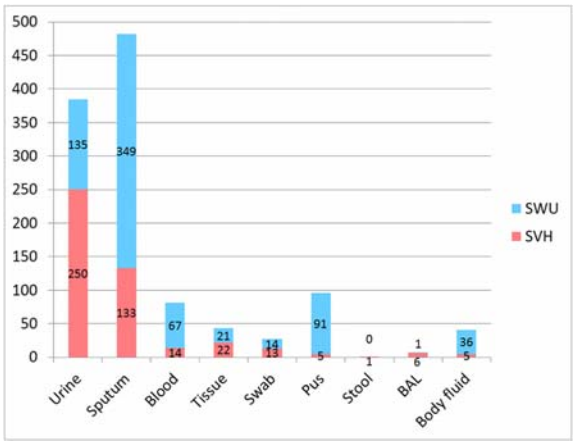

Fig. 1 Specimen distribution (all clinical specimens) n = 1,163 (SVH = 450 specimens; SWU = 713 specimens).

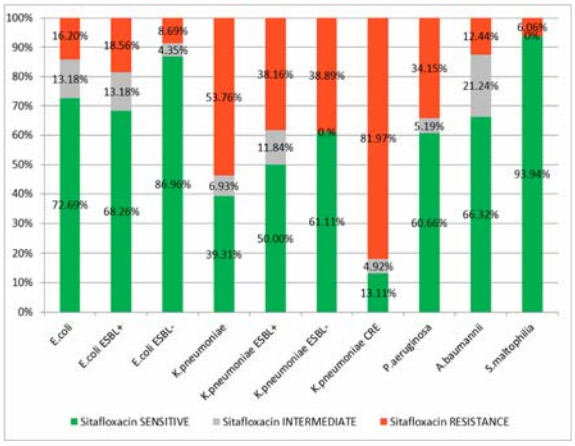

Fig. 2 *In vitro* susceptibility of sitafloxacin from both institutions (*E. coli* = *Escherichia coli*; ESBL = extended-spectrum beta-lactamases; + = positive, - = negative, *K. pneumoniae* = *Klebsiella pneumoniae*; CRE = carbapenem resistant enterobacteriaceae; *P. aeruginosa* = *Pseudomonas aeruginosa*; *A. baumannii* = *Acinetobacter baumannii* and *S. maltophilia* = *Stenotrophomonas maltophilia*).

ceftriaxone (19.91%), amikacin (97.22%), ertapenem (98.6%), imipenem (99.07%), tigecycline (99.5%), and colistin (98.02%) shown in Table 1. *In vitro* susceptibility of ciprofloxacin resistant *E. coli* to sitafloxacin was shown in Table 2. There were 68.62% of all ciprofloxacin resistant *E. coli* susceptible to sitafloxacin. These clinical isolates were from urine (72.69%), sputum (7.87%), blood (5.09%), and other specimens (14.35%).

One hundred sixty seven clinical isolates of *E. coli* had ESBL. The susceptible percentage of sitafloxacin was 68.26%, as comparison with ciprofloxacin (10.78%), ceftriaxone (0%), amikacin (96.41%), ertapenem (100%), imipenem (100%), tigecycline (99.38%), and colistin (97.5%) as shown in Table 1. Majority of the resistant *E. coli* with ESBL to sitafloxacin were found in cases who experienced with sitafloxacin at least once in the past before the collection of clinical specimens. There were 96 isolates of *E. coli* with ESBL that were resisted to ciprofloxacin (total = 149 isolates) and were susceptible to sitafloxacin (64.43%). Similar to overall *E. coli* pattern, most of the clinical specimens were urine (74.85%), followed by sputum (7.19%), blood (5.98%), and other specimens (11.98%).

Thirty-one isolates of *E. coli* with ESBL were resistant to sitafloxacin. Most of them (29 isolates) were from SVH. Seventeen isolates (58.62% of resistant *E. coli* with ESBL to sitafloxacin at SVH) were from patients who previously had been exposed to sitafloxacin at least once.

Only 46 isolates of *E. coli* without ESBL were collected from both institutions. The susceptible percentage of sitafloxacin was 86.96%. The other antibiotics susceptible percentage were ciprofloxacin (17.39%), ceftriaxone (93.48%), amikacin (100%), ertapenem (100%), imipenem (100%), tigecycline (100%), and colistin (100%) as shown in Table 1. Among 83.78% of this *E. coli* that were resistant to ciprofloxacin were susceptible to sitafloxacin. Most of the clinical isolates were from urine (67.39%), sputum (10.87%), blood (2.18%), and all other specimens (19.56%).

Only three isolates of carbapenem resistant enterobacteriaceae (CRE) strain of *E. coli* were included in the present study. Two of them were from SWU and the other was from SVH. These three organisms were all sensitive to sitafloxacin. For ciprofloxacin, two isolates were resistant and one isolate (from SVH) was intermediate.

Overall *K. pneumoniae* (173 isolates: 114 isolates from SVH and 59 isolates from SWU) susceptible percentage of sitafloxacin was 39.31%. This low susceptible result was related to the outbreak of the CRE strain of *K. pneumoniae*, which the majority of these organisms were resistant to sitafloxacin at SWU (54 isolates). The other antibiotics susceptible percentage were ciprofloxacin (15.03%), ceftriaxone (17.92%), amikacin (69.94%), ertapenem (58.74%; 25 isolates of *K. pneumoniae* with ESBL from SVH, one of *K. pneumoniae* without ESBL from SVH, and three isolates of CRE strain of *K. pneumoniae* from SVH were not tested against ertapenem), imipenem (50.29%), tigecycline (78.87%; 31 isolates of *K. pneumoniae* with ESBL from SVH and two isolates of CRE strain of *K. pneumoniae* from SVH were not tested against tigecycline), and colistin (94.74%; all 54 isolates of CRE strain of *K. pneumoniae* from SWU were not tested against colistin) as shown in Table 1. The incomplete data for ertapenem, tigecycline, and colistin susceptibility tests were because these antibiotics were not routinely tested against *K. pneumonia* at the study period. Only 26.76% of ciprofloxacin resistant *K. pneumoniae* were susceptible to sitafloxacin. Although it looked similar to overall *E. coli* pattern, the clinical specimens were urine (53.75%), sputum (27.75%), blood (9.25%), and other specimens (9.25%) but more percentage of clinical specimens were from sputum.

Seventy-six clinical isolates were of *K.*

Table 1. Susceptible percentage of in vitro susceptibility of sitafloxacin (SIT) compared to other antibiotics (CIP = ciprofloxacin, LEV = levofloxacin, CTX = ceftriaxone, CTZ = ceftazidime, AMK = amikacin, ERT = ertapenem, IMI = imipenem, COL = colistin, TIG = tigycycline, TSX = trimethoprim/sulfamethoxazole and SUL = cefoperazone/sulbactam) against *Escherichia coli* (*E.coli*), *Escherichia coli* with extended-spectrum beta-lactamases (*E.coli* ESBL), *Escherichia coli* without ESBL (*E.coli* non ESBL), *Klebsiella pneumoniae* (*K.pneumo*), *Klebsiella pneumoniae* with ESBL (*K.pneumo* ESBL), *Klebsiella pneumoniae* without ESBL (*K.pneumo* non ESBL), CRE strains of *Klebsiella pneumoniae* (*K.pneumo* CRE), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Acinetobacter baumannii* (*A. baumannii*) and *Stenotrophomonas maltophilia* (*S. maltophilia*)

	SIT	CIP	LEV	CTX	CTZ	AMK	ERT	IMI	COL	TIG	TSX	SUL
E. coli (total) n = 216 (SWU = 14, SVH = 202)	72.69	12.04	-	19.91	-	97.22	98.6	99.07	98.02	99.5	-	-
E. coli ESBL n = 167 (SWU = 7, SVH = 160)	68.26	10.78	-	0	-	96.41	100	100	97.5	99.38	-	-
E. coli non ESBL n = 46 (SWU = 5, SVH = 41)	86.96	17.39	-	93.48	-	100	100	100	100	100	-	-
K. pneumo (total) n = 173 (SWU = 114, SVH = 59)	39.31	15.03	-	17.92	-	69.94	58.74 n = 144	50.29	94.74 n = 119	78.87 n = 140	-	-
K. pneumo ESBL n = 76 (SWU = 3, SVH = 73)	50	9.01	-	0	-	96.05	96.08 n = 51	65.79	91.78	74.36 n = 45	-	-
K. pneumo non ESBL n = 36 (SWU = 2, SVH = 34)	61.11	52.78	-	86.11	-	100	100 n = 35	100	100	96.3	-	-
K. pneumo CRE n = 61 (SWU = 54, SVH = 7)	13.11	0	-	0	-	19.67	0 n = 58	1.64	100 n = 7	20 n = 59	-	-
P. aeruginosa n = 366 (SWU = 266, SVH = 100)	60.66	51.37	-	-	60.66	71.31	-	58.74	99.44	-	-	-
A. baumannii n = 386 (SWU = 342, SVH = 44)	66.32	15.54	-	-	-	20.57	-	-	98.46	94.04	-	22.02
S. maltophilia n = 33 (SWU = 3, SVH = 30)	93.94	-	48.48	-	-	-	-	-	-	-	90.91	-

Table 2. *In vitro* susceptibility of comparative quinolone resistant organisms to sitafloxacin

Comparative Quinolone-Resistant	Sitafloxacin-Susceptible	Sitafloxacin-Intermediate	Sitafloxacin-Resistant
Ciprofloxacin			
E. coli (n = 188)	n = 129 (68.62%)	n = 24 (12.77%)	n = 35 (18.61%)
E. coli with ESBL (n = 149)	n = 96 (64.43%)	n = 22 (14.77%)	n = 31 (20.8%)
E. coli without ESBL (n = 37)	n = 31 (83.78%)	n = 2 (5.41%)	n = 4 (10.81%)
K. pneumonia (n = 142)	n = 38 (26.76%)	n = 12 (8.45%)	n = 92 (64.79%)
K. pneumoniae with ESBL (n = 65)	n = 27 (41.54%)	n = 9 (13.85%)	n = 29 (44.61%)
K. pneumoniae without ESBL (n = 16)	n = 3 (18.75%)	n = 0 (0%)	n = 13 (81.25%)
K. pneumonia CRE (n = 61)	n = 8 (13.11%)	n = 3 (4.92%)	n = 50 (81.97%)
P. aeruginosa (n = 146)	n = 16 (10.96%)	n = 13 (8.9%)	n = 117 (80.14%)
A. baumannii (n = 326)	n = 196 (60.12%)	n = 82 (25.15%)	n = 48 (14.73%)
Levofloxacin			
S. maltophilia (n = 9)	n = 9 (100%)	n = 0 (0%)	n = 0 (0%)

pneumoniae with ESBL. Most cases were from SVH (73 isolates). The susceptible percentage of sitafloxacin was 50%. The susceptible percentage of other antibiotics included ciprofloxacin (9.01%), ceftriaxone (0%), amikacin (96.05%), ertapenem (96.08%; 25 isolates from SVH were not tested against ertapenem), imipenem (65.79%), tigecycline (74.36%; 31 isolates from SVH were not tested against tigecycline), and colistin (91.78%) shown in Table 1. Twenty-seven isolates of *K. pneumoniae* with ESBL that were resistant to ciprofloxacin (total = 65 isolates) were susceptible to sitafloxacin (41.54%). The clinical specimens were from urine (59.21%), sputum (27.63%), blood (6.58%), and all other specimens (6.58%).

Only 36 clinical isolates from both institutions (34 isolates from SVH and two isolates from SWU) were *K. pneumoniae* without ESBL. The susceptible percentage of sitafloxacin was 61.11% while the susceptible percentage of ciprofloxacin was 52.78%. The susceptible percentage of other antibiotics included ceftriaxone (86.11%), amikacin (100%), ertapenem (100%; one isolate from SVH was not tested against ertapenem), imipenem (100%), tigecycline (96.3%), and colistin (100%) shown in Table 1. Only three isolates of *K. pneumoniae* without ESBL that were resistant to ciprofloxacin (total = 16 isolates) were susceptible to sitafloxacin (18.75%). Urine was main clinical specimen (50%), followed by sputum (33.33%), blood (5.56%), and other specimens (11.11%).

There were 61 clinical isolates of CRE strain of *K. pneumoniae* (54 isolates from SWU and seven isolates from SVH). The susceptible percentage of sitafloxacin was only 13.11% while the susceptible percentage was 0% for ciprofloxacin shown in Table 2. The susceptible percentage of other antibiotics were 0% for ceftriaxone, 19.67% for amikacin, 0% for ertapenem (three isolates from SVH were not tested against ertapenem), 1.64% for imipenem (an isolate from SWU was sensitive to imipenem but was resistant to meropenem and ertapenem), 20% for tigecycline (two isolates from SVH were not tested against tigecycline), and 100% for colistin (data only from SVH; all 54 isolates from SWU were not tested against colistin) as shown in Table 1. There was an outbreak of CRE strain of *K. pneumoniae* at SWU during the period of the present study. Only seven isolates (12.96%) of CRE strain of *K. pneumoniae* at SWU were susceptible to sitafloxacin, while three isolates (5.56%) were intermediate and 44 isolates (81.48%) were resistance. Urine was main clinical specimen (49.18%) followed by sputum (24.59%), blood (14.75%), and all other specimens (11.48%).

There were 366 isolates of *P. aeruginosa* included in the study from both institutions (266 isolates from SWU and 100 isolates from SVH). The susceptible percentage of sitafloxacin was 60.66% while the susceptible percentage of ciprofloxacin was 51.37%. The susceptible percentage of other antibiotics were 71.31% for amikacin, 60.66% for ceftazidime, 99.44% for colistin, and 58.74% for imipenem as shown in Table 1. The susceptibility of isolates from SVH against sitafloxacin was 55% compared to 36% for ciprofloxacin while the susceptibility of isolates from SWU against sitafloxacin was 62.78% compared to 57.14% for ciprofloxacin. Sixteen isolates of *P. aeruginosa* resistant to ciprofloxacin (total = 146 isolates) were susceptible to sitafloxacin (10.96%). Most of the clinical specimens were from sputum (46.72%) followed by urine (23.22%),

blood (3.01%), and all other specimens (27.05%).

A. baumannii was included in the present study for the 386 isolates (342 isolates from SWU and 44 isolated from SVH). The susceptible percentage of sitafloxacin was 66.32% while the susceptible percentage of ciprofloxacin was 15.54%. The susceptible percentage of other antibiotics were 20.57% for amikacin, 94.04% for tigecycline, 98.46% for colistin, and 22.02% for cefoperazone/sulbactam as shown in Table 1. The susceptible percentage of isolates from SWU to sitafloxacin was 69.01% compared to 15.5% for ciprofloxacin and 16.37% for imipenem while the susceptible percentage of isolates from SVH to sitafloxacin was 45.45% compared to 15.91% for ciprofloxacin. The susceptible percentage of the strains that were resistant to ciprofloxacin was 60.12% for sitafloxacin. Most of the specimens were sputum (61.92%), followed by urine (12.18%), blood (7.51%), and other specimens (18.39%).

Thirty-three isolates of *S. maltophilia* from both institutions were included in the present study. The susceptible percentage of sitafloxacin was 93.94%. The quinolone that was tested for comparison was levofloxacin, which was 48.48% susceptible. Another tested antibiotic was trimethoprim/sulfamethoxazole (TSX), which was 90.91% susceptible, as shown in Table 1. There were nine isolates (27.27%) of *S. maltophilia* resistant to levofloxacin. All of them were susceptible to sitafloxacin. The specimens were sputum (78.79%), urine (9.09%), blood (3.03%), and other specimens (9.09%).

Discussion

Sitafloxacin is a new fluoroquinolone approved in Thailand for treatment of urinary and respiratory infections[1,2]. Tiengrim S et al reported its effective in vitro activities on *E. coli* with ESBL, *K. pneumoniae* with ESBL, *P. aeruginosa*, and carbapenem resistant *A. baumannii* from five medical institutions in Thailand[5]. This important data brought out the possibility of treating these resistant bacterial infections with sitafloxacin.

During the past decade, *E. coli* with ESBL seemed to be the rising causative organism for urinary tract infections[11,12]. Effective oral antibiotics are needed. Around the year 2013, there were only three available oral antibiotics in Thailand that had *in vitro* activity against *E. coli* with ESBL. They were sitafloxacin[5], nitrofurantoin[13-16], and fosfomycin sachet[14-16].

Sitafloxacin has been clinically used as a step down oral antibiotic for complicated urinary tract infections with *E. coli* with ESBL, following initial parenteral antibiotic at SVH since the end of 2012. Malaisri C et al later demonstrated successful step down treatment with sitafloxacin compared to ertapenem[17]. Manosuthi W et al also reported successful sitafloxacin treatment of complicated urinary tract infections and acute pyelonephritis as initial antibiotic[1]. Sitafloxacin is one of the current antibiotics of choice for treating complicated urinary tract infections and respiratory tract infections expected or proved to be caused by resistant bacteria at SVH.

Since the end of 2012, many additional susceptibility tests to sitafloxacin were ordered for cases because of concern of these bacterial infections at SVH. The most common situation would be urinary tract infection that was expected to be caused by *E. coli* with ESBL. Another common scenario would be a situation in which a doctor tried to find an oral antibiotic to treat the resistant bacterial infection that resisted to all available oral antibiotics. This strategy created a lot of *in vitro* susceptibility data to sitafloxacin at SVH.

In contrast to SVH, sitafloxacin was limited used at SWU. Between January and April 2014, Linasmita et al had conducted a study evaluating *in vitro* activities of sitafloxacin for *A. baumannii* and *P. aeruginosa*[18]. These data collection patterns were continued until June 2015. Although limited use of sitafloxacin, SWU had invaluable *in vitro* activities data of sitafloxacin especially for all strain of *A. baumannii* and *P. aeruginosa*. There was also an outbreak of CRE strain of *K. pneumoniae* at SWU during the present study, in which sitafloxacin was tested as a possible treatment. These data collection patterns could explain the distribution of the clinical specimens (more urine at SVH and more sputum at SWU) and the clinical isolates (more *E. coli* and *K. pneumoniae* at SVH whereas more *A. baumannii* and *P. aeruginosa* at SWU) collected from both institutions. There were also less cases of resistant *A. baumannii* and resistant *P. aeruginosa* infections at SVH compared to SWU. Combination of data from both institutions would give adequate data for all strains of the resistant organisms in concern.

Sitafloxacin had reasonable *in vitro* activities for all strains of *E. coli* since the susceptible percentage data from both institutions were 72.69% for overall *E. coli*, 68.26% for *E. coli* with ESBL, 86.96% for *E. coli* without ESBL, and 68.62% of ciprofloxacin resistant *E. coli*. This data would rather be lower susceptible than general *in vitro* sitafloxacin susceptibility data

since data from SVH would be from a cohort that was suspected for resistant *E. coli* infections as its nature of data collection. No strains of *E. coli* were sensitive to ciprofloxacin and resistant to sitafloxacin.

The previous *in vitro* susceptibility of sitafloxacin against 73 isolates of *E. coli* with ESBL from five institutions showed that the susceptibility was 57.5% (minimum inhibitory concentration (MIC) ≤1) and 84.9% (MIC ≤2)[5]. Their antimicrobial susceptibility tests were done by determining for MICs of *E. coli*. According to Jones RN et al, the susceptible breakpoint of MIC 1 microgram/ml or smaller, should be compatible with disk diffusion method with inhibition zone diameter 19 mm or larger, considered to be sensitive and 15 mm or greater, considered to be resistance[9]. The susceptible percentage data of *E. coli* with ESBL in the present study was 68.26% which was higher than previous data. This result might be interpreted that SVH *E. coli* with ESBL strains was less resistant to quinolone in general since the susceptible percentage of ciprofloxacin was 10.78% compared to 9.6% in previous study[5].

There were three strains of CRE strain of *E. coli* which all were susceptible to sitafloxacin. It would be very interesting to further analyze the activity of sitafloxacin against this very resistant strain of *E. coli*. If it was proven to be susceptible, clinical implication should be beneficial.

Another interesting observation from the present study was 58.62% of *E. coli* with ESBL resistant to sitafloxacin were from the persons who previously had been exposed to sitafloxacin at least once. This data suggested that the development of resistance to sitafloxacin can happen after its use. The use of sitafloxacin should be limited to infections with resistant *E. coli* without other available susceptible oral antibiotics. In light of the present data, clinical use of sitafloxacin should be directed by specific susceptibility to it, especially in those patients previously treated with sitafloxacin.

The previous *in vitro* susceptibility of sitafloxacin against 196 isolates of *K. pneumoniae* was 74% (MIC ≤1) and 79.6% (MIC ≤2)[5]. Our *K. pneumoniae* data showed more resistance to sitafloxacin. The main reason was there were more resistant strains of *K. pneumoniae* included in the present study, especially since the outbreak of CRE strains of *K. pneumoniae* at SWU while there were no CRE strain of *K. pneumoniae* included in the previous study. The susceptible percentage of ciprofloxacin against overall *K. pneumoniae* was 15.03% compared to 49.5% in previous study[5] and the susceptible percentage of ciprofloxacin against *K. pneumoniae* with ESBL was 9.25% compared to 20.4% in the previous study[5]. There were also no strains of *K. pneumoniae* sensitive to ciprofloxacin but resistant to sitafloxacin.

For CRE strains of *K. pneumoniae*, the susceptibility of sitafloxacin was only 13.11% while the susceptibility of ciprofloxacin was 0%. Sitafloxacin might not be active against these strains of *K. pneumoniae*. There were 54 SWU isolates of CRE strains of *K. pneumoniae* susceptible to sitafloxacin only for 12.96%. While seven SVH isolates were susceptible to sitafloxacin only for 14.29%. Although sitafloxacin might not have good activity against CRE strains of *K. pneumoniae*, at least some (13.11%) were susceptible as compared to 0% for ciprofloxacin. Sitafloxacin could be helpful in infection with this resistant *K. pneumoniae* with susceptibility proven of its *in vitro* susceptibility test.

The clinical use of sitafloxacin for *K. pneumoniae* should be directed by its individual susceptibility since susceptibility data might varied from institution to institution. Clinicians should prove of its susceptibility before initiation of its clinical use for resistant strains of *K. pneumoniae*. Similar to *E. coli* data, sitafloxacin should be reserved for infections with resistant strains without other available susceptible oral antibiotics.

The susceptible percentage of *in vitro* susceptibility of sitafloxacin against *P. aeruginosa* was 60.66% compared to 55.9% from previous study[5]. The susceptibility of ciprofloxacin was 51.37% compared to 54.9% from previous study[5]. There was 10.96% of *P. aeruginosa* that had ciprofloxacin resistance but was susceptible to sitafloxacin (Table 2). Sitafloxacin might be clinically beneficial for treating the strains of *P. aeruginosa* infections that were resistant to ciprofloxacin but susceptible to sitafloxacin.

Linasmita P et al had presented the SWU data of 93 clinical isolates of *P. aeruginosa* that were 52.7% susceptible to sitafloxacin and 54 isolates of carbapenem-non susceptible *P. aeruginosa* that were 22.2% susceptible to sitafloxacin[18]. There might be a clinical benefit for treating this carbapenem-non susceptible *P. aeruginosa* infections with sitafloxacin after proof of the susceptibility test.

The *in vitro* susceptibility of sitafloxacin against *A. baumannii* was 66.32% compared to 66.9% from previous study[5]. Colistin and tigecycline seemed to have the best susceptible percentage of *in vitro* susceptibilities for *A. baumannii*. The previous SWU

data for 111 isolates of carbapenem resistant *A. baumannii* showed that sitafloxacin had susceptible percentage of in vitro susceptibility at 58.6%[18].

Sitafloxacin was the only available oral antibiotic with proven susceptible of *in vitro* activity for carbapenem resistant *A. baumannii*[5-7]. The limitation of sitafloxacin for carbapenem resistant *A. baumannii* infections was that it had no available parenteral form that would be more beneficial to those who were critically ill.

For *S. maltophilia*, although there were only 33 isolates included to the study, it was interesting that the susceptible percentage of *in vitro* susceptibility of sitafloxacin was 93.94%, higher than that of TSX, which was 90.91%. Although the susceptible percentage of compared quinolone, which was levofloxacin, was 48.48%, there were only nine isolates (27.27%) of *S. maltophilia* that were resistant to levofloxacin. TSX was usually the drug of choice for *S. maltophilia* infections[19]. Although the resistance of *S. maltophilia* to TSX was low, some recent reports have shown their resistance to TSX data[19-21]. Sitafloxacin might be beneficial for treating patients with *S. maltophilia* infections who were allergic to sulfa allergy or had resistance to TSX.

Conclusion

Sitafloxacin had a good susceptible percentage of *in vitro* susceptibility test to all strains of *E. coli*, most strains of *K. pneumoniae* (except CRE strains of *K. pneumoniae*), *P. aeruginosa*, *A. baumannii*, and *S. maltophilia* at SWU and SVH. Sitafloxacin also had more susceptible percentage of *in vitro* susceptibility against *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, and *S. maltophilia* compared to other fluoroquinolones. It should be a considered antibiotic for treatment of urinary and respiratory tract infections caused by the resistant strains of these bacteria with proof of its in vitro susceptibility.

What is already known on this topic?

Sitafloxacin was susceptible against *E. coli* with ESBL, *K. pneumoniae* with ESBL, *P. aeruginosa*, and carbapenem resistant *A. baumannii*.

Sitafloxacin had more susceptible percentage of *in vitro* susceptibility to these bacteria compared to other quinolones.

What this study adds?

Sitafloxacin had a reasonable *in vitro* susceptibility against all strains of *E. coli*, most strains of *K. pneumoniae* (except CRE strains of *K. pneumoniae*), *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*.

Sitafloxacin had more susceptible percentage of *in vitro* susceptibility to *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, and *S. maltophilia* compared to comparative fluoroquinolones.

Most of the ciprofloxacin resistant *E. coli* without ESBL were susceptible to sitafloxacin.

Some CRE strains of *K. pneumoniae* may be susceptible to sitafloxacin.

Around 10% of *P. aeruginosa* resistant to ciprofloxacin were susceptible to sitafloxacin.

Individual *in vitro* susceptibility to sitafloxacin was needed, especially for the cases previously exposed to sitafloxacin to better predict its susceptibility.

Potential conflicts of interest

None.

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ผลการตอบสนองทางห้องปฏิบัติการของยา sitafloxacin กับยาปฏิชีวนะตัวอื่น ๆ ต่อแบคทีเรียที่แยกได้จากผู้ป่วยของโรงพยาบาลศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดาฯ มหาวิทยาลัยศรีนครินทรวิโรฒ และโรงพยาบาลสมิติเวช สุขุมวิท

วรพจน์ ตันติศิริวัฒน์, พัชรสาร ลีนะสมิต

ภูมิหลัง: Sitafloxacin เป็นยาใหม่ในกลุ่ม fluoroquinolone ชนิดรับประทานที่มีใช้ในประเทศไทยสำหรับรักษาการติดเชื้อในระบบทางเดินหายใจและระบบทางเดินปัสสาวะ ผลการวิเคราะห์การตอบสนองทางห้องปฏิบัติการของยานี้ที่ผ่านมาพบว่ายานี้มีความไวต่อเชื้อ Escherichia coli ชนิดที่มีเอ็นไซม์ ESBL, Klebsiella pneumoniae ชนิดที่มีเอ็นไซม์ ESBL, Pseudomonas aeruginosa และ Acinetobacter baumannii ชนิดที่ดื้อต่อยา carbapenem

วัตถุประสงค์: เป็นการรวบรวมข้อมูลย้อนหลังถึงผลการตอบสนองทางห้องปฏิบัติการของยา sitafloxacin ต่อแบคทีเรียที่แยกได้จากผู้ป่วยของโรงพยาบาลศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดาฯ มหาวิทยาลัยศรีนครินทรวิโรฒ (SWU) และโรงพยาบาลสมิติเวช สุขุมวิท (SVH)

วัสดุและวิธีการ: แบคทีเรียที่แยกได้จากผู้ป่วยที่ได้รับการตรวจสอบผลการตอบสนองทางห้องปฏิบัติการต่อยา sitafloxacin ทุกตัวตั้งแต่ เดือนมกราคม พ.ศ. 2557 ถึง เดือนมิถุนายน พ.ศ. 2558 จะถูกนำมาวิเคราะห์ในวิจัยนี้ การตรวจสอบผลการตอบสนองของ sitafloxacin ใช้วิธี disk diffusion โดยใช้ inhibition zone diameter ≥19 มิลลิเมตรถือเป็นตอบสนองต่อยาและ <16 มิลลิเมตรถือเป็นดื้อต่อยา การเปรียบเทียบผลการตอบสนอง ทางห้องปฏิบัติการของยา sitafloxacin กับยาปฏิชีวนะตัวอื่น ๆ จะแยกประเมินเชื้อเป็นชนิด ๆ ไปโดยที่จะวิเคราะห์เฉพาะเชื้อที่มีจำนวนมากกว่า 30 ตัวขึ้นไป

ผลการศึกษา: แบคทีเรียทั้งหมด 1,288 ตัวจากสิ่งส่งตรวจทางคลินิก 1,163 อย่างถูกตรวจสอบผลการตอบสนองทางห้องปฏิบัติการของยา sitafloxacin โดยมี 723 สิ่งส่งตรวจจาก SWU และ 560 สิ่งส่งตรวจจาก SVH สิ่งส่งตรวจที่มีมากที่สุดได้แก่ เสมหะ (482), ปัสสาวะ (385), หนอง (96), เลือด (81) เชื้อแบคทีเรียที่ถูกนำมาวิเคราะห์เปรียบเทียบผลการตอบสนองทางห้องปฏิบัติการต่อยาได้แก่ E. coli, K. pneumoniae, P. aeruginosa, A. baumannii และ Stenotrophomonas maltophilia ผลความไวทางห้องปฏิบัติการของเชื้อ E. coli ทั้งหมด (n = 216) ต่อ sitafloxacin คือ ร้อยละ 72.69 (โดยที่เป็นร้อยละ 68.26 สำหรับ E. coli ชนิด ESBL และร้อยละ 86.96 สำหรับ E. coli ชนิดไม่มี ESBL), ผลความไวทาง ห้องปฏิบัติการของเชื้อ K. pneumoniae ทั้งหมด (n = 173) คือร้อยละ 39.31 (โดยที่เป็นร้อยละ 50 สำหรับ K. pneumoniae ชนิด ESBL, ร้อยละ 61.11 สำหรับ K. pneumoniae ชนิดไม่มี ESBL และร้อยละ 13.11 K. pneumoniae ชนิด CRE), ผลความไวทางห้องปฏิบัติการของเชื้อ P. aeruginosa (n = 366) คือ ร้อยละ 60.66, ผลความไวทางห้องปฏิบัติการของเชื้อ A. baumannii (n = 386) คือ ร้อยละ 66.32 และผลความไวทาง ห้องปฏิบัติการของเชื้อ S. maltophilia (n = 33) คือ ร้อยละ 93.94 Sitafloxacin มีเปอร์เซ็นต์ที่ไวต่อเชื้อทางห้องปฏิบัติการมากกว่า ciprofloxacin สำหรับเชื้อ E. coli ทุกชนิด, K. pneumoniae ทุกชนิด, P. aeruginosa และ A. baumannii และมีเปอร์เซ็นต์ที่ไวต่อเชื้อทางห้องปฏิบัติการมากกว่า levofloxacin สำหรับเชื้อ S. maltophilia ถึงแม้ว่าผลความไวทางห้องปฏิบัติการของ sitafloxacin ต่อ K. pneumoniae ชนิด CRE จะไม่ค่อยดี แต่ยังพบว่าอย่างน้อยร้อยละ 13.11 ที่ยังมีความไวทางห้องปฏิบัติการอยู่เมื่อเทียบกับร้อยละ 0 สำหรับ ciprofloxacin

สรุป: Sitafloxacin มีความไวทางห้องปฏิบัติการต่อเชื้อ E. coli, K. pneumoniae, P. aeruginosa, A. baumannii และ S. maltophilia มากกว่า fluoroquinolones ชนิดเปรียบเทียบ Sitafloxacin น่าจะเป็นยาที่ใช้ในการรักษาการติดเชื้อในระบบทางเดินหายใจและระบบทางเดินปัสสาวะที่เกิดจากเชื้อแบคทีเรียดื้อยาดังกล่าวมาข้างต้นโดยที่ได้รับการยืนยันว่ามีความไวทางห้องปฏิบัติการต่อยา sitafloxacin แล้ว