Research Article

Dysglycemic Effect and Misuse Prevalence of Fluoroquinolones in ICU Diabetic Patients

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Abstract

Introduction: Quinolones are one of the most favourable antimicrobial class for the treatment of various infectious diseases. Their side effects and toxicity profile have been established years ago. Multiple studies reported dysglycemic events occurring in diabetic patients admitted to the ICU taking fluoroquinolones. The aim of this study is to determine if there is indeed a relation between fluoroquinolones and dysglycemia.

Methods and Materials: A retrospective observational study targeting the ICU patients who were administered levofloxacin, ciprofloxacin, and moxifloxacin. This study was performed during the period from April 2019 to September 2019 (6 months) in 5 different hospitals in Alexandria, Egypt. 350 patients' ICU files were chosen randomly, then a total of 68 diabetic ICU admitted patients receiving broad-spectrum fluoroquinolones for more than 2 days were included in the study.

Results: From 68 patients who recruited in our study, 15 patients take fluoroquinolone with no need and they suffer from change in their blood glucose level without any additional benefit. The most misused fluoroquinolone was Levofloxacin, as 73.3% of patients with main diagnosis non-infectious treated with Levofloxacin, and 20% among them suffered from decreased blood glucose level where 13.3 % had significant increase of their blood sugar level.

Conclusion: Dysglycemia caused by fluoroquinolones is an important issue of clinical significance and must be addressed and managed. Dysglycemia occurs by varying degrees and differ between different agents of fluoroquinolones. The effect is more pronounced in diabetics and patients with renal impairment which warrant attention and immediate management. Fluoroquinolone misuse is also another important issue to be addressed as it contributes to increased antimicrobial resistance and exposes the patients to unnecessary side effects some of which might need immediate intervention. Further investigations related to fluoroquinolones prescribing and monitoring is needed to get a better understanding of this existing problem.

Keywords: Anti-infective(s); Fluoroquinolones; Toxicity; Dysglycemia; Adverse Events; Misuse; Diabetes

Abbreviations

ACEIs: Angiotensin Converting Enzyme Inhibitors; AKI: Acute Kidney Injury; B-Blocker: Beta Blocker Drugs; BSL: Blood Sugar Level; CAP: Community Acquired Pneumonia; COPD: Chronic Obstructive Pulmonary Disease; CNS: Central Nervous System; DVT: Deep Vein Thrombosis; DNA: Deoxyribonucleic Acid; HAP: Hospital

Acquired Pneumonia; ICU: Intensive Care Unit; VAP: Ventilator Associated Pneumonia; BSL decrease > 30%: Blood Sugar Level (BSL) Decreases more than 30% from Initial BSL; BSL increase > 30%: Blood Sugar Level (BSL) Increases more than 30% from Initial BSL; BSL (-30% to +30%) change: Blood sugar level (BSL) Decreases Less than 30% or Increases Less than 30 from Initial BSL, that could not Harm Patients; Initial BSL: The first random blood sugar level for each patient at hospital admission as routine laboratory investigation and not by capillary blood glucose method to ensure accuracy of results; Final BSL: The second laboratory random glucose level for the same patient after 2 days fluoroquinolone treatment at least; CYP450: Cytochrome P450

Introduction

Since their discovery 40 years ago, quinolones have been one of the most favourable antimicrobial class for the treatment of various infectious diseases [1-4]. This is because they offer a lot of attributes that made them an ideal class of antibiotics [1-4]. These include their broad spectrum activity, high potency, good bioavailability and availability of both oral and intravenous formulations [2]. Therefore, they are the best choice for physicians to prescribe them in numerous indications, which may cause irrational use of this important class of antibiotics.

The first agent in this class was nalidixic acid which was discovered as a by-product of antimalarial research [1-3]. Quinolone structure represented in figure 1 is not only responsible for its activity but also its side effects profile [1-5]. Over the years, modifications have been made to this basic nucleus to synthesize different numbers of quinolones to improve their properties and overcome antimicrobial resistance [1-5]. Different classes of quinolone antibiotics are represented in figure 2.
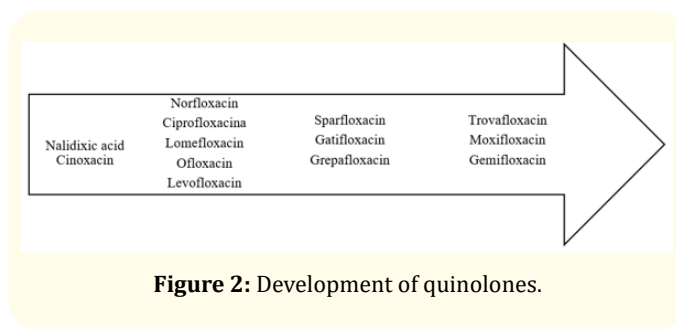

Figure 1: Basic structure of quinolones.

Figure 2: Development of quinolones.

Mechanism of action of quinolones is mainly through inhibition of topoisomerase enzymes (also known as DNA gyrase) specifically topoisomerase II and IV [1-3]. Inhibition of this enzyme prevents DNA replication and thus bacterial multiplication and survival IV [1-3].

Fluoroquinolones are known to have a number of side effects which are unique to this class [4-7]. These side effects range from mild to severe, life threatening side effects class [4-7]. These side effects can be classified according to organ system into cardiovascular, CNS, gastrointestinal, dermatologic, hepatic, renal, musculoskeletal and others [4,6,7]. Examples of some of the common side effects include QTc prolongation, nausea/vomiting/diarrhoea, phototoxicity, renal failure, elevation in hepatic enzymes, hepatitis, seizures and tremors [4,6,7].

Dysglycemia (disturbances in blood glucose levels) have been reported with a number of fluoroquinolones [8]. Both hypoglycaemia and hyperglycaemia have been documented with gatifloxacin which led to label changes [9-12]. Although risk of hypoglycaemia is more common, some reports found that gatifloxacin is also responsible for hyperglycaemia [10,12-14]. other fluoroquinolones as ciprofloxacin, levofloxacin and moxifloxacin have also been associated with hypo- or hyperglycaemic effects which need further attention [12,14-17]. As impact of dysglycemia might not be significant in majority of patients, diabetics are more prone to be affected by this dysglycemic side effect of fluoroquinolones [18-20]. Diabetic patients whether insulin dependent or not are more sensitive to changes in their blood glucose level [18-20]. Thus, any fluctuation in their blood glucose level might lead to deleterious or even life-threatening effects warranting immediate action [18-20]. Another factor which might precipitate to dysglycemia in diabetic patients is the interaction between fluoroquinolones and oral hypoglycaemic agents especially sulfonyl urea [17,21]. Risk factors for dysglyce-

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mia have been identified in various papers including concomitant use of oral hypoglycaemic agents, declined renal functions (renal impairment), body mass index ≤ 30 kg/m^2 and interactions with other drug classes causing hypoglycaemia as beta blockers [14,17].

Despite the main mechanism of dysglycemic effect of fluoroquinolone not well established yet, there are some studies tried to explain it, therefore the mechanism of hypoglycemia may be due to sulphonyl urea-like action, that causes excessive insulin secretion in the first 3 days, then due to pancreatic evacuation of insulin, hyperglycemia may occur in the next two to six days of initiation of quinolones treatment [22]. Another mechanism which may be due to drug-drug interactions through CYP450 isoenzymes or other types of interactions (Ghandour and Azar).

This study is designed to assess the glycaemic changes occurring in diabetic patients during fluoroquinolone treatment and the prevalence of inappropriate prescription of fluoroquinolones in ICU patients. Three fluoroquinolones were included in the study: Ciprofloxacin, Levofloxacin, and moxifloxacin. Demographics and risk factors were identified to detect if significant correlation exist between them and glycaemic changes occurring.

Methods and Materials

Study design and setting

It is a retrospective observational study targeting the ICU patients who were administered levofloxacin, ciprofloxacin, and moxifloxacin. This study was performed during the period from April 2019 to September 2019 (6 months) in 5 different hospitals in Alexandria, Egypt.

Study population

A 350 files of ICU patients in the 5 hospitals were randomly checked, then 180 files are excluded as patients' history are not diabetic. After checking for patients' medications from selected files we exclude 78 files that their treatment did not contain fluoroquinolones. To assess the dysglycemic effect of fluoroquinolones we need two random blood sugar level (BSL) readings from hospital Laboratory, to ensure accuracy of results, one at initiation of fluoroquinolone (Baseline BSL) and the second one at day 3-5 from starting quinolone dose (Final BSL), therefore we exclude 34 files. Then a total of 68 diabetic ICU admitted patients receiving broadspectrum fluoroquinolones for more than 2 days were included in the study. Inclusion and exclusion data are represented in flow diagram (Figure 3).
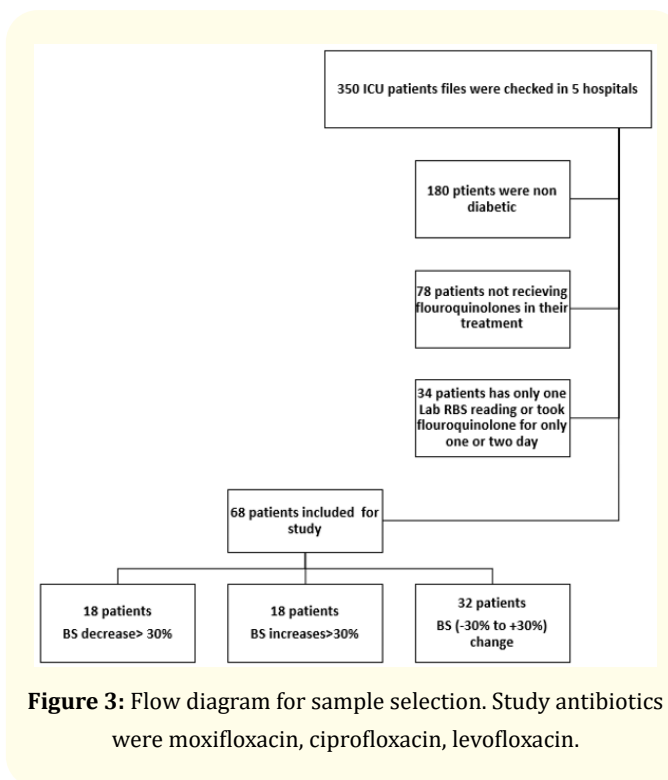

Figure 3: Flow diagram for sample selection. Study antibiotics were moxifloxacin, ciprofloxacin, levofloxacin.

All studied population are patients previously diagnosed as diabetic before ICU admission and they are taken nearly the same nutrition regimens in these ICU units.

Data source and ethics

Data were obtained from Patients' profiles from 5 different hospitals' Databases in Alexandria. Each patient file included the patient's chief complaint, the admission date, past medical history, history of present illness, ICU length of stay, whether the patient is ventilated or not, and all current medications with their doses, and durations of therapy.

Patients' Blood glucose levels were followed up retrospectively from the day the Fluoroquinolone treatment was initiated to the day the patient was discharged from the ICU. Data were obtained after the permission of the responsible crew with regards to ethics and patients' privacy (using the patients' initials and their file number only).

A paper form was prepared to assess the glycaemic changes during the Fluoroquinolone treatment.

The form contained the patients' demographic data, the medical and medication history, the co-administered drugs, the baseline

BSL, ICU length of stay, renal impairment and the final BSL readings. Any change in the BSL during the treatment was recorded and the medical intervention (if present) in case of dysglycemia was mentioned.

Statistical analysis

Data were analysed using the Statistical Package for Social Science (SPSS) ver.23. All qualitative variables are presented as counts and percentages, Chi-squared test and Fischer exact test were used to test for statistical significance. Quantitative variables that were not normally distributed and are reported as medians and interquartile range, Mann-Whitney and Kruskal Wallis tests were used to test for statistical significance. Quantitative variables that were normally distributed and are reported as mean and standard deviation, t-tests were used to test for statistical significance.

Results

Distribution of fluoroquinolone use with patient's diagnosis

Fluoroquinolone treatment was indicated for the resolution of different conditions as in table 1.

Fluoroquinolones used were ciprofloxacin (19.12%), levofloxacin (79.41%) and moxifloxacin (1.47%).

Clinical infectious indications included hospital acquired pneumonia (HAP) (17.6%), Ventilator acquired pneumonia (VAP) (14.7%), Community Acquired pneumonia (CAP) (14.7%), sepsis (4.4%), COPD exacerbation (23.5%).Other non-infectious indications (22.1%), which is a misuse of this important class. That means 15 from 68 patients who recruited in our study take fluoroquinolone with no need and they suffer from change in their blood glucose level without any additional benefit. From table 2 the most misused fluoroquinolone was Levofloxacin, as 73.3% of patients with main diagnosis non-infectious treated with Levofloxacin, and 20% among them suffered from decreased blood glucose level where 13.3 % had significant increase of their blood sugar level.

Distribution of variables with dysglycemia

Qualitative variables

A number of variables have been assessed against changes in blood glucose levels to detect their effect on dysglycemia in patients using fluoroquinolones (Table 3). Variables were gender, and comorbidities as presence or absence of renal impairment, hypertension, ischemic heart disease, systolic heart failure, ventilatory support, in addition to combined antibiotics used and concomitant drugs which can interfere with blood glucose level.

Main diagnosis (Count & %)	Ciprofloxacin	Levofloxacin	Moxifloxacin	% from total indications	P-value
VAP	3 (30%)	7 (70%)	0	10 (14.7%)	
HAP	1 (8.3%)	11 (91.7%)	0	12 (17.6%)	
CAP	1 (8.3%)	10 (83.3%)	1 (83%)	12 (17.6%)	
Sepsis	2 (66.7%)	1 (33.3%)	0	3 (4.4%)	
COPD exacerbation	2 (12.5%)	14 (87.5%)	0	16 (23.5%)	0.209
Non-infectious indication (Cardiac, DVT, AKI, Etc.) (Misuse)	4 (26.7%)	11 (73.3%)	0	15 (22.1%)	
Total	13	54	1	68 (100%)	

Table 1: Fluoroquinolones used and patients' main diagnosis.

*VAP: Ventilator Associated Pneumonia; HAP: Hospital Acquired Pneumonia; CAP: Community Acquired Pneumonia; COPD: Chronic Obstructive Pulmonary Disease; DVT: Deep Vein Thrombosis; AKI: Acute Kidney Injury.

Fluoroquinolones	BSL decrease> 30%	BSL increases> 30%	BSL (-30% to +30%) change	Total
Ciprofloxacin	1 (6.7%)	1 (6.7%)	2 (13.3%)	4 (26.7%)
Levofloxacin	3 (20%)	2 (13.3%)	6 (40%)	11 (73.3%)

Table 2: Misused quinolones and dysglycemia.

*BSL decrease > 30%: Blood sugar level (BSL) decreases more than 30% from initial BSL.

BSL increase > 30%: Blood sugar level (BSL) increases more than 30% from initial BSL.

BSL (-30% to +30%) change: Blood sugar level (BSL) decreases less than 30% or increases Less than 30 from initial BSL, that couldn't harm patients.

Variable (count & %)	BSL decrease> 30%	BSL increases>30%	BSL (-30% to +30%) change	Total	P-value
Gender					
Male	9 (25%)	12 (33.3%)	15 (41.7%)	36	0.387
Female	9 (28%)	6 (19%)	17 (53%)	32	
Renal impairment					
No	11 (24.4%)	12(26.7%)	22 (48.9%)	45	0.859
Yes	7 (30.4%)	6 (26.1%)	10 (43.5%)	23	
Ischemic heart disease					
No	16 (29.1%)	14 (25.5%)	25 (45.5%)	55	0.721
Yes	2 (15.4%)	4 (30.8%)	7 (53.8%)	13	
Systolic heart failure					
No	16 (25.8%)	16 (25.8%)	30 (48.4%)	62	0.642
Yes	2 (33.3%)	2 (33.3%)	2 (33.3%)	6	
Hypertension					0.310
No	14 (32.6%)	11 (25.6%)	18 (41.9%)	43	
Yes	4 (16%)	7 (28%)	14 (56%)	25	
Ventilation					
No	13 (33.3%)	10 (25.6%)	16 (41%)	39	0.308
Yes	5 (17.2%)	8 (27.6%)	16 (55.2%)	29	
Fluoroquinolone					
Ciprofloxacin	2 (15.4%)	3 (23.1%)	8 (61.5%)	13	0.432
Levofloxacin	16 (29.6%)	14 (25.9%)	24 (44.4%)	54	
Moxifloxacin	0	1 (100%)	0	1	
Combined antibiotics used					
Cephalosporins					
None	9 (24.3%)	8 (21.6%)	20 (54.1%)	37	0.585
Cefotaxime	4 (44.4%)	2 (22.2%)	3 (33.3%)	9	
Ceftriaxone	2 (25.0%)	4 (50.0%)	2 (25.0%)	8	
Ceftazidime	3 (21.4%)	4 (28.6%)	7 (50.0%)	14	
Meropenem					
No	12 (24.5%)	13 (26.5%)	24 (49%)	49	0.820
Yes	6 (31.6%)	5 (26.3%)	8 (42.1%)	19	
Linezolid					
No	15 (24.2%)	17 (27.4%)	30 (48.4%)	62	0.391
Yes	3 (50%)	1 (16.7%)	2 (33.3%)	6	
Amikacin					
No	18 (28.1%)	17 (26.6%)	29 (45.3%)	64	0.800
Yes	0	1 (25%)	3 (75%)	4	

Other prescribed drugs that could interfere with Blood sugar level					
B-Blocker					
No	14 (31.1%)	10 (22.2%)	21 (46.7%)	45	0.369
Yes	4 (17.1%)	8 (34.8%)	11 (47.8%)	23	
ACEIs					
No	14 (25.9%)	14 (25.9%)	26 (48.2%)	54	0.999
Yes	4 (28.6%)	4 (28.6%)	6 (42.8%)	14	
Systemic corticosteroids					
No	13 (33.3%)	9 (23.1)	17 (43.6%)	39	0.323
Yes	5 (17.3%)	9 (31%)	15 (51.7%)	29	
Furosemide					
No	7 (23.3%)	7 (23.3%)	16 (53.3%)	30	0.654
Yes	11 (28.9%)	11 (28.9%)	16 (42.1%)	38	
Noradrenalin					
No	17 (26.6%)	18 (28.1%)	29 (45.3%)	64	0.800
Yes	1 (25%)	0	3 (75%)	4	

Table 3: Distribution of qualitative variables with dysglycemia.

Quantitative variables

Quantitative variables including age, ICU days and number of fluoroquinolone treatment days were identified as in table 4 by median and range due to abnormal distribution. Blood glucose changes were identified as more than 30% increase or decrease from initial BSL levels.

Analytical Results:

Data were analysed using the Statistical Package for Social Science (SPSS) ver.23. Tests performed were Kruskal Wallis test (Table 5 and 6). Results of Kruskal Wallis test with a P-value of 0.003 and <0.0005 indicates significant change in initial and final Blood sugar level between dysglycemia classes (Figure 4 and 5) (Table 5). On the other hand (Table 6) and (Figure 6) shows non-significant P-value for Kruskal Wallis test for distribution of blood sugar level percent among Fluoroquinolones used.

Test for correlation was carried out using Spearman's Rho test (Table 7). Results indicate no significant correlation between blood glucose level changes and variables tested (Age, ICU days and fluoroquinolone treatment days) at a level of significance of 0.05 (2-tailed).

Variable (Median and range)	BSL decrease> 30%	BSL increases>30%	BSL (-30% to +30%) change
Age	64.5 (37-82) years	61.5 (48-85) years	64 (42-82) years
ICU Days	8 (3-19) days	8 (4-17) days	8 (2-21) days
Fluoroquinolone treatment days	5 (3-14) days	6 (3-16) days	5 (4-14)

Table 4: Age, ICU days and Fluoroquinolone treatment days.

Variable (Median and range)	BSL decrease> 30%	BSL increases>30%	BSL (-30% to +30%) change	P-value
Initial blood sugar	245 (132-640) mg/dl	184 (76-336) mg/dl	160 (74-450) mg/dl	0.003
Final blood sugar	160 (74-450) mg/dl	342 (160 -685) mg/dl	145 (78-425) mg/dl	<0.0005

Table 5: Relation between initial of final blood sugar level and dysglycemia.

Variable (Median and range)	Ciprofloxacin	levofloxacin	Moxifloxacin	P -value
BSL percent change	-5.55% (-53% to 270%)	- 10% (-58% to 156%)	111%	0.562

Table 6: Relation between blood sugar level percent change and fluroquinolone type.

			Initial BSL	Final BSL	Age	ICU days	Fluoroquinolone days
Spearman's rho	BSL change	Correlation Coefficient	-.332**	.706**	-.007	-.031	.005
		Sig. (2-tailed)	.006	.000	.954	.801	.967
		N	68	68	68	68	68

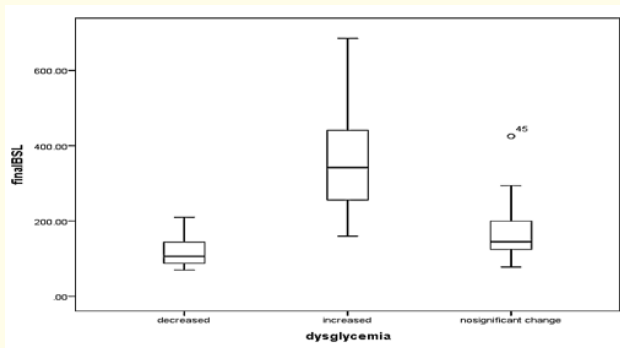**Table 7:** Correlation between quantitative variables with blood sugar level change.

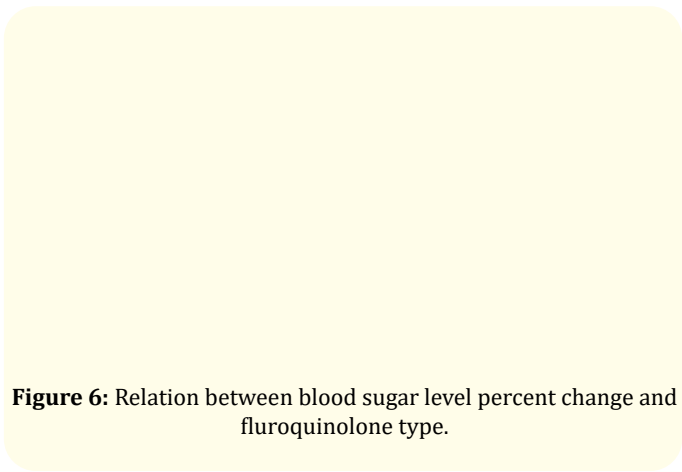**Figure 4:** Relation between initial blood sugar level and dysglycemia.

Figure 5: Relation between final blood sugar level and dysglycemia.

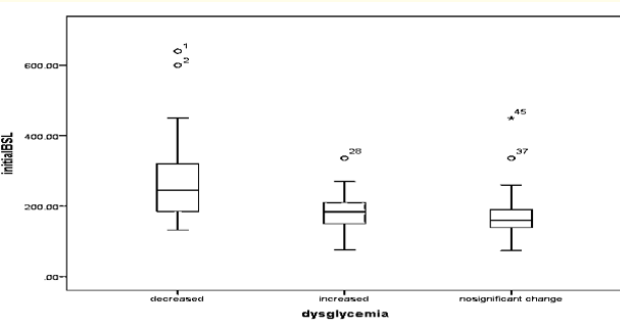**Figure 6:** Relation between blood sugar level percent change and fluroquinolone type.

Discussion

Fluoroquinolones are an important class of antibiotics used in various infectious clinical conditions [1-4]. Apart from their toxicity profile causing QTc prolongation, tendinitis, phototoxicity, renal and liver damage, these antimicrobials offer a great option as treatment of many infections [1-4]. Therefore, their use needs to limit for a suitable indication, and any misuse can harm patients from unwanted adverse effects, in addition to, increase percentages of multidrug resistant organisms. Reports of dysglycemia with quinolone therapy have been increasing in the last years whether hypo- or hyperglycaemia [9,11-17]. Disturbances in blood glucose levels is an important aspect that must be taken into consideration when prescribing such antibiotics especially in diabetics or patients with renal impairment [14,17-20].

We conducted a study to assess dysglycemic effect of three fluoroquinolones which are ciprofloxacin. levofloxacin and moxifloxacin. Our findings proved that those fluoroquinolones are associated with dysglycemia whether hypo- or hyperglycaemia with varying degrees as shown in figure 7. As shown in the graph, Levofloxacin is more associated with dysglecmia than cipro- and moxifloxacin. Moxifloxacin has the lowest incidence of dysglycemia. Moxifloxacin causes only hyperglycemia. Ciprofloxacin causes both increase and decrease in BSL but nonsgnificant changes is of higher incidence which might reflect that it has no significant effect on blood glucose levels as compared to the other two agents. Correlation between age, ICU stay and days of fluoroquinolones treatment and the incidence of dysglycemia was assessed, with no siginficatnt results.
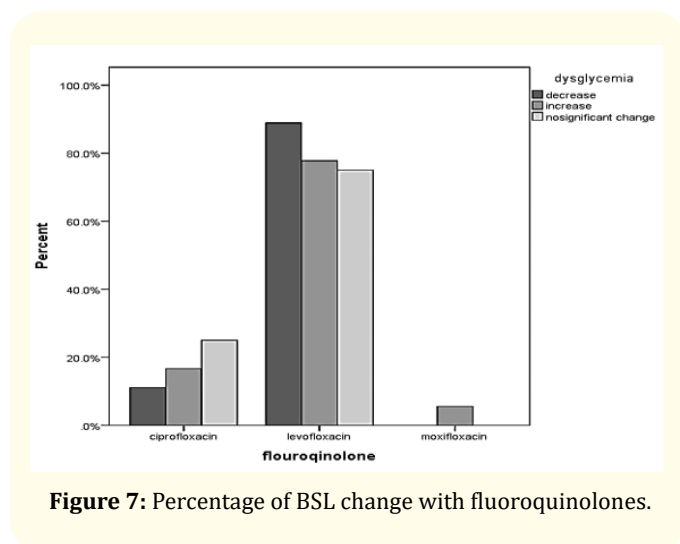

Figure 7: Percentage of BSL change with fluoroquinolones.

To date, the actual mechanism of hypo- and hyperglycemia caused by fluoroquinolone is not quite clear. Studies have investigated the mechanism of hypoglycemia caused by fluoroquinolones. Studies showed that mechanism of hypoglycemia caused by fluoroquinolones is through inhibition of adenosine triphosphate dependant potassium channel in beta-cells of Ilets of Lanagerhans in pancereas [23,24]. This in turn will case depolarization of beta-cells memberane. Depolarization will cause voltage-dependant calcium channels to open leading to calcium influx pancereas [23,24]. Calcium cause insulin secretion which in turn leads to derease in blood glucose level (hypoglycemia) [23,24]. These effects seen when fluoroquinolones used on short term. On long term, insulin synthesis decresases and distintegration of insulin secondary to oversecretion during the short term phase takes place [14-17]. Thus, hyperglycemia takes place. This is mechanism for hyperglycemia is still an assumption yet to be proved.

To date, gatifloxacin is the only fluoroquinolone which has a proven dysglycemic effect and has already been warranted label changes [9-13]. As the dysglycemic effect is dose dependant, dose modifications in renal impairment is warranted [14,17]. Reports have been increasing concerning the dysglycemic effects of othr fluoroquinolones as levofloxacin, ciprofloxacin and moxifloxacin [12,14-17]. This lead to the hypothesis that this dysglycemia is a class effect. Yet studies so far can't prove this hypothesis as dysglycemic events vary between different fluoroquinolones [12]. More studies into this aspect are warranted.

Another issue that should be addressed is fluoroquinolones misuse. Fluoroquinolones are being prescribed for non-infectious/non-bacterial indications which accounts for emerging resistance [25,26]. These antibiotics should be reserved for specific organisms which are resistant to other antibiotics. Other ways of misuse include longer than appropriate duration of use, repeated antimicrobial coverage, inadequate coverage, empiric use of fluoroquinolones as in urinary tract infections (asymptomatic bacteriuria) [25,26]. All this leads to fluoroquinolone resistance together with unnecessary side effects that reduce the quality of patients' life [25,26]. Thus, appropriate prescription and audit of fluoroquinolones is warranted.

Conclusion

In conclusion, fluoroquinolones are an important class of antibiotics used in the treatment of various ailments. Toxicity profile has been established years ago and well-known. Dysglycemia caused by fluoroquinolones is an important issue of clinical significance and must be addressed and managed. Dysglycemia occurs by varying degrees and differ between different agents of fluoroquinolones. The effect is more pronounced in diabetics and patients with renal impairment which warrant attention and immediate management. Further investigations related to dysglycemia and its mechanism is needed to get a better understanding of this problem.

Study Limitations

This study targeted diabetic patients, as they are more sensitive to any change in blood sugar level, but further studies are needed to describe fluoroquinolones dysglycemic effect on other populations. Due to limited number of patients that recruited in the study, we could not clearly prove the association between fluoroquinolones use and hypo- or hyperglycaemia.

Conflict of Interest

None.

Appendix

Patient	Gender	Diagnosis	Quinolone used	Initial BSL	Final BSL	% change	Quinolone treatment days
1	Male	HAP	Ciprofloxacin	450	210	-53.33%	5
2	Female	Non infectious (cardiac, renal impairment, etc.)	Ciprofloxacin	185	113	-38.92%	12
3	Female	VAP	Ciprofloxacin	176	270	53.41%	3
4	Male	CAP	Ciprofloxacin	240	525	118.75%	7
5	Female	Non infectious (cardiac, renal impairment, etc.)	Ciprofloxacin	185	685	270.27%	16
6	Male	sepsis	Ciprofloxacin	134	100	-25.37%	13
7	Male	Non infectious (cardiac, renal impairment, etc.)	Ciprofloxacin	450	425	-5.56%	5
8	Male	COPD exacerbation	Ciprofloxacin	139	115	-17.27%	7
9	Female	VAP	Ciprofloxacin	200	180	-10%	4
10	Male	COPD exacerbation	Ciprofloxacin	139	120	-13.67%	7
11	Male	VAP	Ciprofloxacin	160	160	0%	14
12	Female	sepsis	Ciprofloxacin	94	121	28.72%	6
13	Female	Non infectious (cardiac, renal impairment, etc.)	Ciprofloxacin	229	270	17.90%	3
14	Male	Non infectious (cardiac, renal impairment, etc.)	Levofloxacin	640	95	-85.16%	4
15	Male	Non infectious (cardiac, renal impairment, etc.)	Levofloxacin	600	95	-84.17%	4
16	Male	COPD exacerbation	Levofloxacin	300	82	-72.67%	14
17	Female	CAP	Levofloxacin	320	133	-58.44%	8
18	Male	COPD exacerbation	Levofloxacin	299	144	-51.84%	4
19	Male	HAP	Levofloxacin	322	197	-38.82%	6
20	Female	sepsis	Levofloxacin	239	118	-50.63%	5
21	Female	COPD exacerbation	Levofloxacin	220	100	-54.55%	12
22	Female	CAP	Levofloxacin	188	70	-62.77%	5
23	Female	CAP	Levofloxacin	251	149	-40.64%	10
24	Female	HAP	Levofloxacin	270	170	-37.04%	5
25	Male	HAP	Levofloxacin	225	130	-42.22%	4
26	Male	CAP	Levofloxacin	170	88	-48.24%	3
27	Female	CAP	Levofloxacin	154	76	-50.65%	13
28	Female	Non infectious (cardiac, renal impairment, etc)	Levofloxacin	132	77	-41.67%	3
29	Male	COPD exacerbation	Levofloxacin	148	100	-32.43%	13
30	Male	CAP	Levofloxacin	84	160	90.48%	6
31	Female	VAP	Levofloxacin	270	354	31.11%	7
32	Female	Non infectious (cardiac, renal impairment, etc)	Levofloxacin	138	229	65.94%	5
33	Male	HAP	Levofloxacin	161	256	59.01%	7

34	Male	CAP	Levofloxacin	203	305	50.25%	4
35	Male	Non infectious (cardiac, renal impairment, etc)	Levofloxacin	76	195	156.58%	8
36	Male	HAP	Levofloxacin	214	360	68.22%	6
37	Male	COPD exacerbation	Levofloxacin	336	500	48.81%	6
38	Female	HAP	Levofloxacin	210	375	78.57%	4
39	Male	CAP	Levofloxacin	150	318	112%	6
40	Female	VAP	Levofloxacin	160	330	106.25%	4
41	Male	COPD exacerbation	Levofloxacin	183	420	129.51%	9
42	Male	VAP	Levofloxacin	197	441	123.86%	7
43	Male	COPD exacerbation	Levofloxacin	210	500	138.10%	5
44	Female	Non infectious (cardiac, renal impairment, etc)	Levofloxacin	336	294	-12.50%	5
45	Male	COPD exacerbation	Levofloxacin	260	220	-15.38%	5
46	Male	VAP	Levofloxacin	190	150	-21.05%	12
47	Female	Non infectious (cardiac, renal impairment, etc)	Levofloxacin	165	128	-22.42%	8
48	Female	CAP	Levofloxacin	190	159	-16.32%	5
49	Female	Non infectious (cardiac, renal impairment, etc)	Levofloxacin	140	110	-21.43%	3
50	Male	COPD exacerbation	Levofloxacin	150	120	-20%	9
51	Female	Non infectious (cardiac, renal impairment, etc)	Levofloxacin	163	138	-15.34%	5
52	Female	HAP	Levofloxacin	160	140	-12.50%	3
53	Male	COPD exacerbation	Levofloxacin	148	130	-12.16%	14
54	Female	HAP	Levofloxacin	155	140	-9.68%	4
55	Female	HAP	Levofloxacin	165	150	-9.09%	8
56	Male	VAP	Levofloxacin	145	130	-10.34%	2
57	Female	VAP	Levofloxacin	150	138	-8%	5
58	Male	CAP	Levofloxacin	189	190	0.53%	3
59	Male	HAP	Levofloxacin	197	200	1.52%	7
60	Female	Non infectious (cardiac, renal impairment, etc)	Levofloxacin	74	78	5.41%	5
61	Female	COPD exacerbation	Levofloxacin	200	210	5%	4
62	Male	COPD exacerbation	Levofloxacin	117	130	11.11%	6
63	Male	COPD exacerbation	Levofloxacin	190	204	7.37%	2
64	Female	VAP	Levofloxacin	106	120	13.21%	5
65	Female	Non infectious (cardiac, renal impairment, etc)	Levofloxacin	190	207	8.95%	5
66	Female	HAP	Levofloxacin	120	150	25%	9
67	Male	COPD exacerbation	Levofloxacin	160	200	25%	5
68	Male	CAP	Moxifloxacin	118	249	111.02%	6

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