ABSTRACT:

Background:

Levofloxacin and ciprofloxacin are more commonly used among fluoroquinolone class and the question of cardiac safety and dysglycemia of this class has been raised.

Objective:

To compare intravenous levofloxacin and ciprofloxacin regarding their risk on QTc prolongation and dysglycemia in diabetic and non-diabetic patients.

Methods:

A randomized prospective study at Beni-Suef university hospital was conducted on 200 adult patients over six months. The patients received intravenous levofloxacin 750mg once daily or ciprofloxacin 400mg twice daily. Electrocardiogram and fasting blood glucose were obtained from each patient before starting antibiotic, 24 hours, 72 hours after the first dose, and 72 hours after antibiotics cessation.

Results:

The present study showed that levofloxacin administration produced a significant prolongation of QTc interval compared to the ciprofloxacin group after 72 hours of starting treatment in diabetic patients. The relative risk for QTc prolongation with levofloxacin was more than ciprofloxacin by about 4 and 1.5 times in diabetic and non-diabetic patients, respectively. Levofloxacin administration showed a significant elevation of ALT and AST, 72 hours after the first dose compared to baseline values in diabetic patients. Levofloxacin administration produced significant hyperglycemia, 72 hours after the first dose compared to ciprofloxacin in diabetic patients, while levofloxacin administration produced significant hyperglycemia, 24 hours after the first dose compared to ciprofloxacin in non-diabetic patients. Levofloxacin administration revealed significant hypoglycemia, 72 hours after the first dose compared to

ciprofloxacin in non-diabetic patients. The relative risk for dysglycemia with levofloxacin was 2.28 and 1.39 times more than ciprofloxacin in diabetic and non-diabetic patients, respectively.

Conclusion:

The present study showed that the risk for QTc prolongation and hyperglycemia was greater with levofloxacin than ciprofloxacin in diabetic and non-diabetic patients. In addition, the risk for hypoglycemia was greater with levofloxacin than ciprofloxacin in non-diabetic patients.

Keywords:

Ciprofloxacin, Levofloxacin, QTc-prolongation, Dysglycemia, Diabetic and Non-diabetic

List of publication:

Nada A. Saad, Ahmed A. Elberry, Hazem Samy Matar, Raghda R. S. Hussein (2021). Effect of ciprofloxacin vs levofloxacin on QTc-interval and dysglycemia in diabetic and non-diabetic patients. The International Journal of Clinical Practice.

DOI: 10.1111/ijcp.14072.

List of Abbreviations

ADA	The American Diabetes Association
AECB	Acute exacerbations of chronic bronchitis
ALT	Alanine transaminase
AST	Aspartate transaminase
ATP	Adenosine triphosphate
AUC	The area under the concentration
CAP	Community-acquired pneumonia
CDAD	Colstridium difficile-associated diarrhea
CG	Cockcroft and Gault formula
CI	Confidence interval
CrCl	Creatinine clearance
CRR	The counter-regulatory response
CYP1A2	Cytochrome P450 isoenzyme 1A2
DM	Diabetes mellitus
ECG	Electrocardiogram
EAD	Early after depolarization
FAERS	FDA Adverse Event Reporting System
FDA	The Food and Drug Administration
GABA	γ-aminobutyric acid
GDM	Gestational diabetes mellitus
GLUT 1	Glucose transporter 1
HAP	Hospital-acquired pneumonia
I_{k1}	The inward-rectifier background current
I_{Kr}	The rapid component of the delayed rectifier potassium current

I_{ks}	The slow component of the delayed rectifier potassium current
I_{kur}	The ultrarapid outward current
Ito	The transient outward current
$I_{to,f}$	The fast, transient outward current
$I_{to,s}$	The slow, transient outward current
K	Potassium
Mg	Magnesium
MIC	Minimal inhibitory concentration
Na	Sodium
NMDA	N-methyl-D-aspartate
QTc	The corrected QT interval
RR	Relative risk
SD	Standard deviation
Tdp	Torsade de pointes
VF	Ventricular fibrillation

Acknowledgement

First of all, thanks to **God** for everything and for helping me to finish this study.

I am sincerely and deeply grateful to **Dr. Ahmed Abdullah Hassan Elberry** ; Professor of Clinical Pharmacology, Faculty of Medicine, Beni-Suef University for his instructive supervision, valuable guidance, unlimited help and advice during this work.

I am very grateful for **Dr. Hazem Samy Hussein**; Lecturer of Internal Medicine Faculty of Medicine, Beni-Suef University for his help during my work and for allowing me to collect the patients in the intermediate care unit at Beni-Suef University Hospital.

I would like to express my sincere gratitude and heartily gratefulness to **Dr. Raghda Roshdy Sayed Hussein**; Lecturer of Clinical Pharmacy, Faculty of Pharmacy, Beni-Suef University for her fruitful and continuous advice and encouragement and supervision during this work.

I would like to thank the physicians and nursing staff in Beni-Suef University Hospital.

Deep thanks to the patients included in the thesis for their great cooperation. Without their help, I could not have done this thesis.

Thanks

Nada Abd El-Hamed

March, 2021

List of figures

Figure 1.1: QT interval 1

FIGURE 1.2: Corrected QT interval using Bazett's formula 1

Figure 1.3: Cardiac action potential (Briasoulis et al., 2011) 5

Figure 1.4: Mechanisms of drug induced TdP. The hERG channel (left) was blocked by drug that can result in prolonged QT (middle) and TdP (right; upper panel), that can lead to ventricular fibrillation (VF) (right; lower panel) (Van Noord et al., 2010). 7

Figure 1.5 : The counter-regulatory response (CRR) to hypoglycemia . 11

Figure 1.6: Diabetic complications (Skyler et al., 2017). 18

Figure 1.7: Common structure of 4-quinolones (Emami et al., 2010). Error! Bookmark not defined.

Figure 1.8: ciprofloxacin (Jacoby and Hooper, 2012) 32

Figure 1.9: Levofloxacin (Silvia, 2014) 37

Figure 1.10: ECG of a normal QT interval and QT interval prolongation (Trinkley et al., 2013). 41

Figure 2.1 Follow-up of the study patients 46

Figure 3.1 Effect of administration of Ciprofloxacin and Levofloxacin on QTc prolongation in diabetic patients. * considered significant at p <0.05 compared to ciprofloxacin. 49

Figure 3.2 Effect of administrating Ciprofloxacin and Levofloxacin on QTc prolongation in non-diabetic patients. 50

Figure. 3.3 Effect of administration of Ciprofloxacin and Levofloxacin on hyperglycemia in diabetic patients. * considered significant at p <0.05 compared to ciprofloxacin. 55

Figure 3.4 Effect of administration of Ciprofloxacin and Levofloxacin on hyperglycemia in non-diabetic patients. * considered significant at p <0.05 compared to ciprofloxacin. 55

Figure. 3.5 The relative risk for QTc prolongation, hyperglycemia and hypoglycemia in diabetic patients after the administration of Ciprofloxacin and Levofloxacin.* considered significant at p <0.05 compared to ciprofloxacin. 56

Figure. 3.6 The relative risk for QTc prolongation, hyperglycemia and hypoglycemia in non-diabetic patients administrating Ciprofloxacin and Levofloxacin. * considered significant at p <0.05 compared to ciprofloxacin. 56

Figure 3.7 The effect of ciprofloxacin on dysglycemia in diabetic and non-diabetic patients regarding hours.*considered significant at $P < 0.05$ compared to baseline value 58

Figure 3.8 The effect of levofloxacin on dysglycemia in diabetic and non-diabetic patients regarding hours.* considered significant at $P < 0.05$ compared to baseline value. 59

Figure 3.9 Effect of administration of Ciprofloxacin and Levofloxacin on hypoglycemia in diabetic patients. * considered significant at p <0.05 compared to ciprofloxacin 60

Figure 3.10 Effect of administration of Ciprofloxacin and Levofloxacin on hypoglycemia in non-diabetic patients. * considered significant at p <0.05 compared to ciprofloxacin 60

List of tables

Table 1.1: List of some drugs that induce QTc prolongation **4**

Table 1.2: The American Diabetes Association and the Endocrine Society classification of hypo-glycemia in diabetes **9**

Table 1.3: Classification of hypoglycemia according to the glucose level Error! Bookmark not defined.

Table 1.4: Causes of hypoglycemia in diabetic and non-diabetic patients **12**

Table 1.5: Causes of hyperglycemia in diabetic and non-diabetic patients Error! Bookmark not defined.

Table 1.6: Classification of diabetes **19**

Table 1.7: Classification of fluoroquinolones **24**

Table 1.8: Pharmacokinetic properties of ciprofloxacin and levofloxacin **25**

Table 1.9: Summarized uses of ciprofloxacin in infectious diseases Error! Bookmark not defined.**34**

Table 3.1: Baseline characteristics of Ciprofloxacin and Levofloxacin groups regarding demographics, and laboratory data **48**

Table 3.2: Comparison between ciprofloxacin and levofloxacin regarding their risk on QTc prolongation: **49**

Table 3.3: Comparison of QTc between each group regarding times: Error! Bookmark not defined.

Table 3.4: comparison between laboratory results within ciprofloxacin groups at baseline, 24 hours, 72 hours after antibiotic use, and 72 hours after antibiotic cessation: 52

Table 3.5: comparison between laboratory results within levofloxacin groups at baseline, 24 hours, 72 hours after antibiotic use, and 72 hours after antibiotic cessation: 53

Table 3.6: Comparison between ciprofloxacin and levofloxacin regarding their risk on dysglycemia : 54