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The Protective Effect of Lactobacillus against Ciprofloxacin and Levofloxacin Associated Diarrhea in Sample of Iraqi Patients

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Abstract

Fluoroquinolones drugs are important classes of wide spectrum antibacterial agents that are active against a wide range of Gram-negative and Gram-positive pathogens; they are divided into four generations. Specific types of antibiotics have been associated with side effect like diarrhea, this called (collateral damage), which may occur due to drug-resistant organisms and the unwanted development of colonization or infection with multidrug-resistant organisms. This damage is mostly related to levofloxacin and Ciprofloxacin. The aim of the current study was to compare the incidence of collateral damage between two quinolone antibiotic derivatives (ciprofloxacin and levofloxacin) and to evaluate the activity of lactobacillus to reduce the collateral damage. This study was carried out on 100 patients. Administration of ciprofloxacin, levofloxacin each alone or in combination with lactobacillus; the character of diarrhea and the grade of diarrhea was studied before and after 10 days of administration each dosing protocol. The results for this study, there are a significant increase in the incidence of diarrhea for all groups when comparison between before and after treatment diarrhea was made; a number of patients with diarrhea in group 1 after finish the treatment was not significantly higher when compared with group 2 *($P>0.05$)*; meanwhile, number of patients with diarrhea in group 4 after finish the treatment was significantly lower when compared with group 3 *($P<0.05$)*. it can concluded that , The use of ciprofloxacin and levofloxacin associated with incidence of collateral damage represented as diarrhea and levofloxacin is the least risk of this damage, and using of lactobacillus with levofloxacin was better results than the other three groups.

Key words: Collateral damage, Ciprofloxacin, Levofloxacin, Lactobacillus.

تقييم التاثير الوقائي للاكتوباسيلاس ضد الاسهال المصاحب لاستعمال السبروفلوكساسين و الليفوفلوكساسين في عينة من المرضى العراقيين

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الخلاصة

تعد أدوية الفلوروكوينولون من الأنواع المهمة من مضادات البكتيريا الواسعة الطيف والتي تمتلك فعالية ضد البكتريا الموجبة الغرام والبكتريا السالبة الغرام وتقسم الى اربعة أجيال. أنواع محددة من المضادات الحيوية أرتبطت بتأثير جانبي مثل الاسهال, هذا مايعرف بالضرر الجانبي الذي يحصل نتيجة لعضيات مقاومة للدواء وتطور غير مرغوب به للاستيطان أوعدوى مع عضيات مقاومه لعدة أدوية. هذا الضرر هو معظمه يتعلق بالسبروفلوكساسين والليفوفلوكساسين.

ان الهدف من الدراسة الحالية هو لمقارنة امكانية ظهورالاضرار الجانبية بين مضادين حيويين مشتقين من مجموعة الكوينولون (سبروفلوكساسين و ليفوفلوكساسين) وتقييم فعالية اللاكتوباسلس في تقليل ظهورالاضرار الجانبية .هذه الدراسة تم تنفيذها على مائة مريض. تم اعطاء أدوية السبروفلوكساسين او الليفوفلوكساسين بشكل مفرد أو مع اللاكتوباسلس, تم دراسة حالة الاسهال وتدرجات الأسهال درست قبل وبعد عشرة أيام من أعطاء الجرعة المتفق عليها. اظهرت النتائج ان هناك زيادة معنوية في حدوث الأسهال لكل المجاميع عند المقارنة فيما بين قبل وبعد معالجة الأسهال, ان عدد المرضى الذين يعانون من الأسهال في المجموعة الأولى بعد نهاية المعالجة هو أعلى معنويا بالمقارنة مع المجموعة الثانية ($P<0.05$), وان عدد المرضى الذين يعانون من الاسهال في المجموعة الرابعة هو أقل معنويا عند المقارنة بالمجموعة الثالثة ($P<0.05$). ان استخدام السبروفلوكساسين والليفوفلوكساسين ارتبط بحدوث الاضرار الجانبية المتمثلة بالاسهال و الليفوفلوكساسين هو الاقل خطرا من حيث الضرر, وان أستخدام اللاكتوباسلس مع الليفوفلوكساسين أعطى افضل النتائج بخلاف المجاميع الثلاث الاخرى.

الكلمات المفتاحية: الاضرار الجانبية, سبروفلوكساسين, ليفوفلوكساسين, لاكتوباسلس.

Introduction

Fluoroquinolones are synthetic drugs having broad spectrum of antibacterial activity and they are broadly used to treat or prevent infectious diseases [(1)]. They are greatly active against both Gram-positive and Gram – negative microorganisms and have metabolic properties that are promising for treating extensive types of infections; they are active against *Streptococcus pneumonia*, *Mycoplasma pneumoniae*, *Chlamydophila pneumonia* and *Pseudomonas aeruginosa* [(2)].

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Furthermore, fluoroquinolones inhibited either -DNA gyrase, which is an adenosine triphosphate-hydrolyzing topoisomerase II enzyme to keep safe the state of supercoiling in replicating and non-replicating chromosomes of bacteria or -action of topoisomerase IV [3].

Moreover, fluoroquinolones indicated for the treatment of different types of infections like urinary tract infections, chronic bacterial prostatitis, acute uncomplicated cystitis in females [4], skin and skin-structure infections, bone and joint infections [5] and -gastrointestinal infections [6].

Ciprofloxacin is a second-generation fluoroquinolone, is carboxylic acid derivatives of fluoroquinolones, and the most beneficial and it is widely used among fluoroquinolone drugs [7].

Levofloxacin is a third generation fluoroquinolone which is the optical S-(-) isomer of ofloxacin. Levofloxacin have an extended antibacterial range and new different uses when compared with older generations of fluoroquinolone [8, 9].

Antibiotic associated diarrhea is a most important type of collateral damage that associated with the uses of specific type of antibiotics. The major causes of this adverse effect are the presence of drug-resistant organisms and the inadequate development of colonization or occurrence of multidrug-resistant pathogens [10, 11].

Lactobacilli are live bacterial agents without any adverse effects [12]. Lactobacillus considered a probiotics which use as a dietary supplements. Lactobacillus containing different types of bacteria including (Lactobacillus species, Bifidobacterium species, and others). The clinical use of lactobacillus was supports health by improving the normal flora of the gastrointestinal tract (GIT) [13]. Moreover, Lactobacillus can also compete with microorganisms for food and adhesion places on the gastrointestinal mucosa [14]. Besides probiotics can regulate local and systemic immune responses by enhancing the secretion of immunoglobulin IgA [15].

The aim of the current study was to compare the incidence of diarrhea associated with the use of two quinolone antibiotic derivatives (ciprofloxacin and levofloxacin) and evaluate the protective activity of lactobacillus against diarrhea associated with these two antibiotics.

Patients and Methods

Patients

The current prospective study was carried out on 100 patients who diagnosed by gynecologist or urologist or internist having one type of infections which is either typhoid fever , urinary tract infections or gynecological diseases during August 2018 to March 2019. The age of patients range from (18-60) years.

Study design

A prospective study of cohort of 100 patients, divided as:

* Group 1- include 25 patients, taking ciprofloxacin (ciprodar) [R] 500mg tablet twice daily for 10 day [16].

* Group 2- includes 25 patients, taking ciprofloxacin (ciprodar) [R] 500 mg tablet twice daily [16] plus lactobacillus (Vitalactic B) [R] 50 mg capsule twice a day for 10 days [17].

* Group 3- include 25 patients, taking levofloxacin (Tavanic) [R] 250 mg tablet twice daily for 10 days [16].

* Group 4- include 25 patients, taking levofloxacin (Tavanic) [R] at dose 250 mg tablet twice daily [16] plus lactobacillus (Vitalactic B) [R] 50 mg capsule twice a day for 10 days [17]

Inclusion Criteria

The Inclusion criteria for this study were:

1- Patients did not use antibiotic for last three months

2- Patients did not have diarrhea

3- Patients in both sexes at age range from (18-65) years

Exclusion Criteria

The exclusion criteria for this study were:

1- Patients with bowel diseases like (irritable bowel syndrome).

2- Patients in at age less than 18.

3- Patient with allergic reaction against fluoroquinolone.

Diarrhea grade

Diarrhea grade was divided as follow (grade 1 less than 4 times /day over baseline, grade 2 between 4-6 times /day over baseline, grade 3 more than 7 times /day over baseline, grade 4 life-threatening diarrhea [18].

Statistical analysis

All results were expressed as frequencies for each category with calculation of percent for each frequency. Data were analyzed by utilizing computerized statistical package for the social sciences (SPSS) program version 24. Chi square test was performed for test groups to evaluate dependency, if P values < 0.05 were considered to be significantly dependent.

Ethical consideration

All patients included in this study were informed about the aim of the study and they agree to participate in this study and their consent was obtained.

Results

Characteristics of diarrhea

Table 1 and figure 1 showed that, in group 1 there are a significant differences in the presence of diarrhea when comparison was made between patients before starting treatment protocols (4%) and after finishing the treatment protocol (68%) *(P<0.05).*

Moreover, in group 2, there are significant differences in the presence of diarrhea when comparison was made between patients before stating treatment protocols (4%) and after finishing the treatment protocol (44%) *(P<0.05)*.Table 1 and figure 1.

Furthermore, table 1 and figure 1 showed that in group 3, there are significant differences (*P*<0.05) in the presence of diarrhea when comparison was made between patients before stating treatment protocols (0%) and after finishing the treatment protocol (44%).

Moreover, in group 4, there are significant differences in the presence of diarrhea when comparison was made between patients before stating treatment protocols (4%) and after finishing the treatment protocol (24%) (P<0.05).

Table 1. The presence of diarrhea in patients before and after a specific medication protocol.

		Patients with diarrhea	Patients without diarrhea	*P-Value*
Group 1	**Before**	1(4%)	24(96%)	5.31E-05
	After	17(68%)	8(32%)	
Group 2	**Before**	1(4%)	24(96%)	0.0132
	After	11(44%)	14(56%)	
Group 3	**Before**	0(0%)	25(100%)	0.0117
	After	11(44%)	14(56%)	
Group 4	**Before**	1(4%)	24(96%)	0.0415
	After	6(24%)	19(76%)	

- Number of patients for each group =25, chi square test use to evaluate the dependency in the presence of diarrhea before treatments and after the treatment in the study groups

* Group 1 taking ciprofloxacin 500mg tablet twice daily for 10 day.
* Group 2 taking ciprofloxacin 500 mg tablet twice daily plus lactobacillus 50 mg capsule twice a day for 10 days
* Group 3 taking levofloxacin 250 mg tablet twice daily for 10 days
* Group 4 taking levofloxacin at dose 250 mg tablet twice daily plus lactobacillus 50 mg capsule twice a day for 10 days

- The value between two brackets represents a percent of patients with or without diarrhea.

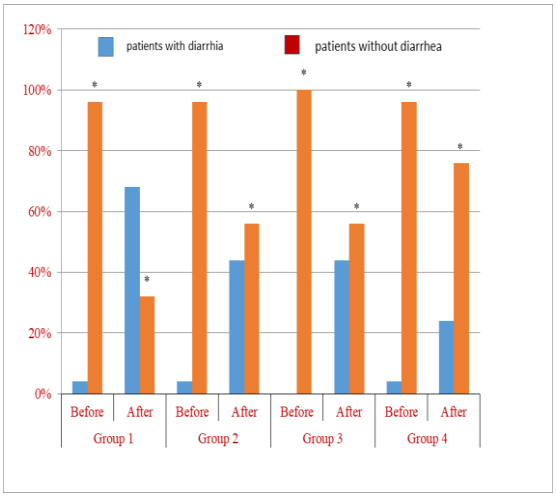

Figure 1. Incidence of diarrhea before and after a specific medication protocol .

Group 1 patients taking ciprofloxacin 500mg tablet twice daily for 10 day.
Group 2 patients taking ciprofloxacin 500 mg tablet twice daily plus lactobacillus 50 mg capsule twice a day for 10 days
Group 3 patients taking levofloxacin 250 mg tablet twice daily for 10 days
Group 4 patients taking levofloxacin at dose 250 mg tablet twice daily plus lactobacillus 50 mg capsule twice a day for 10 days.

Table 2 showed that in group 1, the number of patients having diarrhea after the end of treatment was (17 patients) which is higher when compared to group 2 patients (11patients). Furthermore, there are a significant differences in the presence and absence of diarrhea in group 1 as compare to patients in group 2 (*P<0.05*). Moreover, in group 3, a number of patients having diarrhea was (11 patients) after the end of treatment which is higher when compared with group 4 in which the number of patient having diarrhea was (6 patients). Additionally, there are significant differences (*P<0.05*) in the presence and absence of diarrhea in group 3 as compare to patients in group 4.

Table 2. Comparison in the incidence of diarrhea for patients after taking either ciprofloxacin or levofloxacin with patients taking ciprofloxacin and lactobacillus or levofloxacin and lactobacillus.

	Patients with diarrhea	Patients without diarrhea	*p-value*
Group 1	17	8	0.0873752
Group 2	11	14	
Group 3	11	14	0.0005764
Group 4	6	19	

-Data express as total number of patients, N=25, chi square was use to evaluate the dependent between two study group in which ($p<0.05$) considered as significant dependence

* Group 1 taking ciprofloxacin 500mg tablet twice daily for 10 day.
* Group 2 taking ciprofloxacin 500 mg tablet twice daily plus lactobacillus 50 mg capsule twice a day for 10 days.
* Group 3 taking levofloxacin 250 mg tablet twice daily for 10 days
* Group 4 taking levofloxacin at dose 250 mg tablet twice daily plus lactobacillus 50 mg capsule twice a day for 10 days
- The value between two brackets represents a percent of patients with or without diarrhea.

Table 3showed that in group 1, a number of patients having diarrhea was (17) after the end of treatment; meanwhile, in group 3 (11 patients) having diarrhea; and, there are no significant differences (*P>0.05*) in the presence and absence of diarrhea in group 1 as compared to that in group 3 patients. Additionally, table 3 showed that, in group 2, number of patients having diarrhea was (11) after the end of treatment; meanwhile, in group 4 (6 patients) having diarrhea; and, there are no significant differences in the presence and absence of diarrhea in group 2 as compared to that in group 4 patients (P>0.05).

Table 3. Comparison in the incidence of diarrhea for patients after taking ciprofloxacin with levofloxacin and patients taking ciprofloxacin plus lactobacillus with patient taking levofloxacin plus lactobacillus.

	Patients with diarrhea	Patients without diarrhea	*p-value*
Group 1	17	8	0.087375
Group 3	11	14	
Group 2	11	14	0.135515
Group 4	6	19	

-Data express as total number of patients, N=25, chi square was use to evaluate the dependent between two study group in which ($p<0.05$) considered as significant dependence

* Group 1 taking ciprofloxacin 500mg tablet twice daily for 10 day.
* Group 2 taking ciprofloxacin 500 mg tablet twice daily plus lactobacillus 50 mg capsule twice a day for 10 days.
* Group 3 taking levofloxacin 250 mg tablet twice daily for 10 days
* Group 4 taking levofloxacin at dose 250 mg tablet twice daily plus lactobacillus 50 mg capsule twice a day for 10 days
- The value between two brackets represents a percent of patients with or without diarrhea.

Discussion

The fluoroquinolone class of antimicrobial agents which is active against an extensive range of multi-resistant microorganisms due to its mode of action against different molecular targets than other antibacterial classes [19].

Antibiotic associated diarrhea or collateral damage considered a serious adverse effect associated with the use of fluoroquinolones antibiotic therapy; such type of adverse effect had especial concern when initiating empirical antibiotic therapy, especially in patients who are seriously immune-compromised or ill [20].

In tables 1, 2, and 3, all the groups of patients have a diarrhea after finishing the treatments protocol and this induction was significant differences when compare with same group before the treatment protocol started, besides the addition of lactobacillus to the ciprofloxacin show a not-significant improvement in the diarrhea but the addition of lactobacillus to the levofloxacin show a significant improvement in the induction of diarrhea when compared to levofloxacin alone. At the same time in (Table 4), there are significant differences in the grade of diarrhea in groups1, 2, 3 and 4 when

compare between before start treatment and after finish the treatment protocol.

Margaret EM, *et al* at 2003 showed that drugs belong to fluoroquinolone group may have the ability to prompt diarrhea [(21)].

Probiotics (live microorganisms) can give a health advantages on the host when taken in a sufficient amounts [(22)]. Authors mentioned that the purpose behind taking probiotics in gastrointestinal disorders is based on the theory that probiotics may help in normalization of an unbalanced flora in GIT. Moreover, probiotics may promote intestinal health by the induction of immunity, competition for nutritional components of foods, or the inhibition of epithelial invasion [(23)].

The clinical study for Lactobacillus showed that it had the ability to prevent many clinical conditions, such as the treatment of lactose intolerance and the prevention and treatment of nosocomial diarrhea [(24)]. Guandalini S, *et al* (2000) reported that when lactobacillus has been used in adults and children having an acute diarrhea and treated with lactobacillus, the recurrence of diarrheal symptoms were reduced [(25)]. Results of the current study are matched with those of previous one; where, the use of ciprofloxacin and levofloxacin alone associated with increasing the incidence of diarrhea and at the same time, ciprofloxacin has the ability to induce diarrhea higher than that produced by levofloxacin as seen in table 2; furthermore, the addition of lactobacillus to the treatment protocol caused reduction in the incidence of diarrhea in each treatment (groups 2 and 4), and the reduction in the incidence was significantly higher in group 4 when compared to the incidence of diarrhea in group 2. The same findings have been seen concerning the grade of diarrhea.

Conclusions

The use of ciprofloxacin and levofloxacin associated with increasing the incidence of collateral damage represented as diarrhea; and levofloxacin produced the least risk of this damage; and the use of lactobacillus with levofloxacin produced better results.

References

1. Robicsek A, Strahilevitz J, Jacoby G A, et al. Fluoroquinolone-modifying enzyme: A new adaptation of a common aminoglycoside acetyltransferase. Nature Medicine 2006; 12(1): 83-88.
2. John SB, Mary AJ. The Use of Systemic and Topical Fluoroquinolones. The American academy of pediatrics 2011; 128(4):1034-1045.
3. Hooper DC. Mode of Action of Fluoroquinolones. Drugs 1999;58 (2):6-7
4. Andriole VT. Overview of Quinolone Development, the Quinolones: Past, Present, and Future. CID 2005; 41: S113–9.
5. Prabodh CS, Ankit J, Sandeep J, et al. Ciprofloxacin: Review on developments in synthetic, analytical, and medicinal aspects. Journal of Enzyme Inhibition and Medicinal Chemistry 2010; 25(4): 577-589
6. Schaad UB. Fluoroquinolone antibiotics in infants and children. Infect Dis Clin North Am. 2005; 19(3):617-28.
7. Fatima R Abdul, Nehad A Taher, Ashraf S Hassan, Enaam H Batah. The Effect of Coumarin Derivatives (compounds) on the Vibrio cholerae Isolates from Different Clinical Iraqi Sources. Iraqi J Pharm Sci 2017; 26 (1):32-39
8. Une T, Fujimoto T, Sato K, et al. In vitro activity of Dr-3355, an optically active ofloxacin. Antimicrob Agents Chemother. 1988; 32(9):1336-1340.
9. Fu KP, Lafredo SC, Foleno B, et al. In vitro and in vivo antibacterial activities of levofloxacin (1-ofloxacin), an optically active ofloxacin. Antimicrob Agents Chemother. 1992; 36(4):860-866.
10. Paterson DL. Collateral Damage from Cephalosporin or Quinolone Antibiotic. CID. 2004; 38(4):341-345.
11. Borgmann S. Ciprofloxacin: One Drug – Numerous Collateral Damages. J Bacteriol Parasitol. 2012; 3(6):1000e107
12. Gregor R. The Importance of Guidelines in the Development and Application of Probiotics. Current Pharmaceutical Design 2005; 11(1): 11-16
13. Beverly CM, Clarence EC. Constipation, Diarrhea, and Irritable Bowel Syndrome. In: Chisholm-Burns M. A., Schwinghammer T.L. (eds). Pharmacotherapy Principles & Practice. 4th ed. Mc Graw Hill Education 2016; 21: 333-348
14. Lee YK, Puong KY, Ouwehand AC, Salminen S. Displacement of bacterial pathogens from mucus and Caco-2 cell surface by lactobacilli. J. Med. Microbiol. 2003; 52: 925–30.
15. Ali MM, Emad MM, Nawal MJ, Zeinab R. A Comparative Biochemical Study of Proteins Profile in Iraqi Children and Adolescent with? Thalassemia. Iraqi J Pharm Sci 2010; 9(2):19-23
16. Cheol K, Jieun K, Dae WP, Baek NK, U-Syn H, Seung L, et al. Clinical practice guidelines for the antibiotic treatment of community-acquired urinary tract infections. Journal of Infection and Chemotherapy 2018; 50(1):67-100
17. Hyun JS, Jin Y K, Sung AJ, Seong EK, Hye SP, Yoolwon J, et al. Effect of Probiotic Lactobacillus (Lacidofil ® Cap) for the Prevention of Antibiotic-associated Diarrhea : A Prospective , Randomized, Double-blind, Multicenter Study. J Korean Med Sci. 2010; 25 (12): 1784-1791
18. Zijun HS, huang YS, Hubin H, et al. A systematic review and meta-analysis of the risk

of diarrhea associated with vandetanib treatment in carcinoma patients. Onco. Targets and Therapy 2016; 9:3621–3631

19. Hooper DC. New uses for new and old quinolones and the challenge of resistance. Clin Infect Dis. 2000; 30:243–54.

20. Paterson DL. Collateral damage from cephalosporin or quinolone antibiotic therapy. Clin Infect Dis. 2004; 38 (4):S341-5

21. Margaret EM, Anthony DH, Eli P, et al. Fluoroquinolone Use and Clostridium difficile–Associated Diarrhea. Emerg Infect Dis. 2003; 9(6): 730–733

22. Goldenberg JZ, Lytvyn L, Steurich J, et al. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database Syst. Rev. 2015: Cd004827.

23. 23-Rolfe RD. The role of probiotic cultures in the control of gastrointestinal health. J. Nutr. 2000; 130: 396s–402s

24. Shaukat A, Levitt MD, Taylor BC, et al. Systematic review: effective management strategies for lactose intolerance. Ann Intern Med. 2010; 152: 797-803.

25. Guandalini S, Pensabene L, Zikri MA, Dias JA, et al. Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial. J Pediatr Gastroenterol Nutr. 2000; 30: 54-65