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Immunomodulator Effects of Azithromycin, Ciprofloxacin and Ceftriaxone on Cross - Reaction between Widal Test and Anti-Helicobacter Pylori Igm in Acute Typhoid Fever

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Abstract: ***It has been well known that some antibiotics and other chemotherapeutic agents' poses in addition to their antibacterial activity some other effects, like immunomodulation that improve long term outcome effects in chronic inflammatory disorders. The aims of present the study were evaluation the immunomodulation effects of azithromycin, ciprofloxacin and ceftriaxone on cross reactivity between widal and anti-helichobacter pylori in acute typhoid fever therapy. Thirty newly diagnosed typhoid fever patients, the patients divided into three groups:group (A): treated with azithromycin 500mg /day, group (B):treated with ciprofloxacin 500mg/day, group (C):treated with ceftriaxone 1g/day, the duration of therapy was 14 days then after two weeks a second 10 ml venous blood samples were collected for determinations the differential effects of drugs on cross reactivity between Widal test and anti-helicobacter pylori antibodies after two weeks of treatment termination. Both azithromycin and ciprofloxacin lowers anti-helicobacter pylori and Widal test IgM but ceftriaxone only decreased IgM related to Widal test but not to anti-helicobacter pylori. Conclusion: Azithromycin, ciprofloxacin and ceftriaxone modulates and attenuate Widal test cross reactivity with anti-helicobacter pylori IgM.***

Keywords: azithromycin, ciprofloxacin, ceftriaxone, cross- reaction

1. Introduction

It has been well known that some antibiotics and other chemotherapeutic agents possess in addition to their antibacterial activity some immunomodulation effects that facilitate and progress the long term outcome effects in chronic inflammatory disorders [1].

Macrolides antibiotics accomplish high intracellular concentration with good efficacy against gram positive and negative bacteria as well they inhibit endogenous chemotactic factor leading to the inhibition of bacterial cell membrane and inflammatory signaling pathway interactions, these effects may be related to the down regulation and inhibition of protein kinase A which suppress neutrophil oxidant functions [2, 3].

Moreover, azithromycin inhibit transduction pathway via alterations of neutrophil phosphohydrolase and phospholipase D enzymes this may be attributable to effects on gene expression, thus azithromycin produced immunomodulatory effects on lipoposaccharide by means of inhibition of LPS –mRNA expression which inhibit production of immunoglobulins from plasma cells [4].

Ciprofloxacin is prototype of fluoroquinolone which showed a significant in *vitro* and in *vivo* immunomodulating activity via reticence of inflammatory mediators and proiflammatotry cytokines from activated monocytes, the process of inhibition done through suppression of signal transduction pathway of activated protein kinase [5] furthermore, ciprofloxacin inhibit nitric oxide production induced by cytokine released from lung epithelial cells through down regulation of the JNK signal pathway which not showed with azithromycin, therefore, ciprofloxacin inhibit bacterial induced cytokine production and immune augmentation during acute bacterial infection, as well, it inhibit production of IL-1 from activated macrophage [6].

Ceftriaxone is a B-lactam bactericidal antibiotic that lack the anti-inflammatory and immunomodulator possessions because it stimulate chemotaxis and promote phagocytosis leading to strong antibacterial activity via shifting toward proinflammatory response, during induction of the production of, IL-2, IL-4 and IL-6 all these lead to immunostimulation [7].

All these drugs are renowned in therapy of acute typhoid fever and may be efficient in the management of helicobacter pylori infections [8]

Typhoid fever was a chief public problem lead to severe systemic infection caused by salmonella typhi and paratyphoid bacteria, diagnosed by Widal test which is reliable, simple test depend on IgM and IgG antibodies

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against specific salmonella surface antigens, consequently, Widal-IgM detect early diagnosis and it is highly sensitive but not specific since it cross react with other antigens on other bacteria as in helicobacter pylori and its specificity was 19% for typhoid fever, while blood culture mainly specific for diagnosis of typhoid fever [9].

Therefore, the association between blood culture and anti-IgM was unreliable in most studies and false negative for anti-IgM may occurre in immunosuppressant patients, accordingly Widal test should be explained in concerning with clinical presentation [10].

The Widal test detects serum IgM against lipopolysaccharide O or flagella antigens in acute typhoid fever within 6-8 day of infection, the causes of false positive Widal test may include vaccination, typhus, malaria helichobacter pyloi infection and bacteremia [11].

While false negative Widal tests may be due to using of preceding antibiotic and immunosuppression [12].

Highly specific test for salmonella infection called Tyhidot test (ELISA) that detect both IgM and IgG against outer membrane protein (OMP) with the intention of a good concert in the diagnosis of typhoid fever [13].

However, the Widal test remains the cheapest one in the diagnosis of typhoid fever in developing countries and because of it cross reactivity with anti-helichobacter pyloi antibodies, and for that reason, the aims of present the study was the evaluation the immunomodulation effects of azithromycin, ciprofloxacin and ceftriaxone on cross reactivity between Widal and anti-helichobacter pylori in acute typhoid fever diagnosis and therapy.

2. Material and Methods

This study, prepared in Department of Clinical Pharmacology, College of Medicine, Al-Mustansiriyia University, in collaboration with Department of Microbiology, College of Science, Baghdad University during March 2015, Iraq -Baghdad. The study established and confirmed by inveterate specific scientific committee board and scientific jury.

Thirty newly diagnosed typhoid fever patients (20 males and 10 females), with age ranged from 20-42 years were selected, then venous blood samples were collected and after centrifugation, Widal test kit (Rapid Widal Test Kit, Bio Lab Diagnostic India Private Limited) was used for detection of IgM and IgG against lipopolysacharid O and H antigens, and at the same time blood samples used for screening anti-helicobacter pylori antibodies (Anti-H.pylori IgMAccu Bind, ELISA Kit, India) to asses cross reactivity this was regarded as pretreatment control.

The patients divided into three groups: Group (A): treated with azithromycin 500mg /day, Group (B):treated with ciprofloxacin 500mg/day, Group (C):treated with ceftriaxone 1g/day, the duration of therapy was 14 days then after two weeks a second 10 ml venous blood samples were collected for determinations the differential effects of drugs on cross reactivity between Widal test and anti-helicobacter pylori antibodies after two weeks from treatment termination.

3. Statistical Analysis

The statistical products and service solution (SPSS) version 19 program was used for all analysis.Results are presented as mean±SD with standard error (SE), the data were analyzed via paired t-test, ANOVA and Fisher's test, the significance differences was regarded when *p* value <0.05 as lowest limit of significance.

4. Results

The majority of patients enrolled in this study are younger age group 20-29 years with 53% males and 47% females, all were positive for Widal test (anti O and anti H) figures (1, 2).

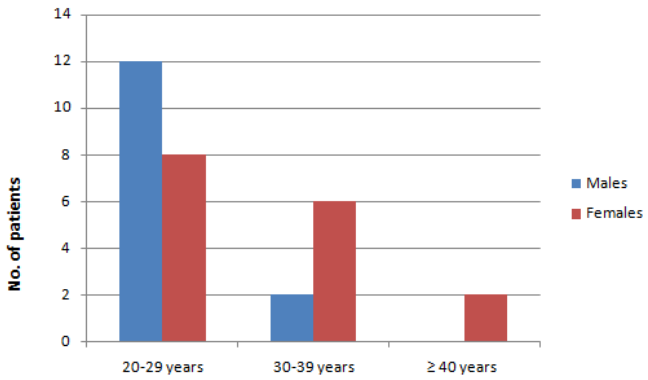

Figure 1: Age and sex distribution of cases in current study

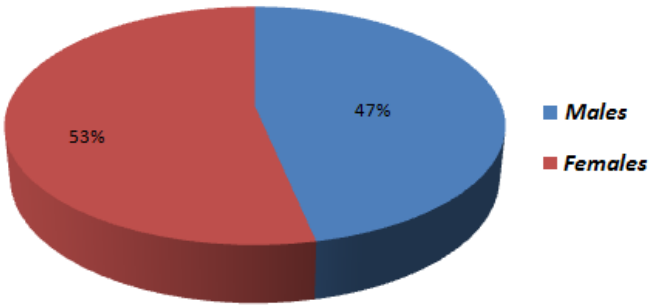

Figure 2: The distribution of cases in current study according to gender

During pretreatment (at diagnosis time) the numbers of positive for Widal test IgM was 19 and 6 patients for IgG while for anti-helicobacter pylori IgM was 30 patients, commonly, these numbers decline significantly after treatment (4 weeks duration) p=0.002, this give an idea about the relationship between Widal test and anti-helicobacter pylori antibodies table (1).

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Table 1: The association between Widal's test antibodies (IgM and IgG) and anti- H. pylori IgM antibody. (n=30)

	No. of positive Widal's test (IgM) cases	No. of positive Widal's test (IgG) cases	No. of positive Anti-H. pylori (IgM) cases	P-value (Chi-square test)
Before treatment	19	6	30	0.002**
After treatment	1	0	22	

** Highly Significant

The connection between Widal test IgM and anti-helicobacter pylori IgM before and after treatment was highly significant p=0.002 table (2).

Table 2: The relationship between Widal's test IgM antibody and anti- H. pylori IgM antibody. (n=30)

	No. of positive Widal's test (IgM) cases	No. of positive Anti-H. pylori (IgM) cases	P-value (Chi-square test)	P-value (Fisher's test)
Before treatment	19	30	0.002**	0.0018**
After treatment	1	22		

** Highly Significant

Whereas, the link between Widal test IgG and anti-helicobacter pylori IgM before and after treatment was less significant p=0.043 table (3).

Table 3: The relationship between Widal's test IgG antibody and anti- H. pylori IgM antibody. (n=30)

	No. of positive Widal's test (IgG) cases	No. of positive Anti-H. pylori (IgM) cases	P-value (Chi-square test)	P-value (Fisher's test)
Before treatment	6	30	0.043*	0.073
After treatment	0	22		

* Significant effect

The immunomodulation effects of antibiotics on antibodies concentrations revealed via lessening of specific antibody concentration. The effects on anti-helicobacter pylori IgM concentration appears after four weeks duration, azithromycin produced significant reduction in the concentration of anti-helicobacter pylori IgM, it lower antibody concentration from 69.3 ± 15.6 to 38.2 ± 13.9 U /ml with 20.55 – 41.65 95% confidence interval p<0.0001. Ciprofloxacin fashioned significant reduction in the concentration of anti-helicobacter pylori IgM, it lower it from 72.4 ± 6.9 to 42.8 ±11.5 U /ml with 23.72– 35.48 confidence interval p<0.0001. Although, ceftriaxone produced insignificant effects in reduction of anti-helicobacter pylori IgM concentration after four weeks duration of therapy from 73.9 ± 9.3 to 71.4 ± 9.3U /ml with -7.3 – 12.3 confidence interval p=0.57 table (4).

Table 4: Comparison between H. pylori IgM concentrations of the group treated with azithromycin before and after 4 weeks of treatment. (n=10)

Mean IgM concentration (U/ml)± SD	Before treatment	After treatment	Standard Error (S.E.)	Paired T-test (df = 9)	95% Confidence interval	P-value
Azithromycin	69.3 ± 15.6	38.2 ± 13.9	4.66	6.67	20.55 – 41.65	<0.0001*
Ciprofloxacin	72.4 ± 6.9	42.8 ± 11.5	2.6	11.38	23.72– 35.48	<0.0001*
Ceftriaxone	73.9 ± 9.3	71.4 ± 9.3	4.33	0.57	-7.3 – 12.3	0.57

* Highly Significant

Regarding Widal test IgM concentration, azithromycin decline it from 0.035 ± 0.012 to 0.0078 ± 0.0042 U /ml with -0.035 – -0.019 confidence interval p<0.0001 also, ciprofloxacin decreased it from0.03 ± 0.01 to 0.0068 ± 0.0041 U /ml with -0.03 –0.015 confidence interval p<0.0001 at the same time as, ceftriaxone lessen the Widal test IgM concentration from 0.0143 ±.0059 to 0.0084 ± 0.0036 with -0.009 –0.0025 confidence interval p=0.0034 table (5).

Table 5: Comparison between Widal'sIgM concentrations of the group treated with ceftriaxone before and after 4weeks of treatment. (n=10)

Mean IgM concentration (U/ml)± SD	Before treatment	After treatment	Standard Error (S.E.)	Paired T-test (df = 9)	95% Confidence interval	P-value
Azithromycin	0.035 ± 0.012	0.0078 ± 0.0042	0.004	7.47	-0.035 – -0.019	<0.0001*
Ciprofloxacin	0.03 ± 0.01	0.0068 ± 0.0041	0.003	6.74	-0.03 – 0.015	<0.0001*
Ceftriaxone	0.0143 ±.0059	0.0084 ± 0.0036	0.002	3.94	-0.009 – 0.0025	0.0034*

* Highly Significant

Therefore, both azithromycin and ciprofloxacin lowers anti-helicobacter pylori and Widal test IgM other than ceftriaxone only decreased IgM related to Widal test but not to anti-helicobacter pylori.

5. Discussion

The antibiotics used in the present study (azithromycin, ciprofloxacin and ceftriaxone) decreases serum level of IgM of both salmonella and helicobacter pylori significantly, which indicates an immunomodulation effect of these antibiotics principally on Widal test.

The antibiotics are frequently interacting with the immune system and bacterial pathogens lead to an assortment of immunomodulation effects on host innate immunity [14].

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Azithromycin produced significant effects in reduction of anti-salmonella and anti-helicobacter pylori IgM.

Moreover, Balaji et al 2014 in vitro studies demonstrated that macrolides activate, stimulate monocyte differentiations, neutrophil chemotaxis effects, and augment macrophage-killing capacity [15].

Furthermore, azithromycin restrain lymphocyte proliferations, suppress the response from T-cell and inhibit IL-1 production from macrophage, consequently it inhibits innate immune response with a straight line or indirectly throughout suppression of lymphocyte proliferations [16].

The probable effects of azithromycin on the immune reaction are of enormous importance with regard treatment or vaccination via targeting the humoral immunity during inhibition of antibody production [17].

Additionally, Sjölund-Karlsson et al 2011 study showed that azithromycin up regulate cell mediated immunity threshold via changes in bacterial flora and preserving intestinal mucosal surface contents thus, it suppresses the immune response for antibody production during vaccination or acute bacterial infections [18].

In general, macrolides suspend antibody response induced by polysaccharide antigen like hepatitis B and pneumococcal polysaccharides leading to lower IgM concentration as compared with B-lactam antibiotics or control these effects may be due to inhibition of antibody production from plasma cell or through elimination the activation of T-cell independent antigen [19]. Furthermore, Yokota et al 2014 study showed that macrolides reduces serum concentration of IgG in respect to vaccine through inhibition of antigen presenting cells or suppression the releasing of co-stimulatory cytokines [20].

Since, the specific immune response is regulated through differentiation of najve T cell into Th1 or Th2 that mainly antigenic load dependent, Th1 secret interferon which activate cell mediated immunity whereas Th2 secret IL-4 which arouse humoral immunity[21] subsequently ciprofloxacin effects shows through lessening in the serum concentration of IgM alongside anti-salmonella and anti-helicobacter pylori IgM.

Animal studies demonstrated that ciprofloxacin inhibit IgM production in mice due to attenuation of delayed type hypersensitivity reaction, declining T-cell cytokine expressions devoid of changes in Th1/Th2 ratio while, azithromycin increase Th1/Th2 ratio with inhibition of IL-4 expression only [22].

Therefore, both ciprofloxacin and azithromycin produced significant immunomodulation effects and attenuate the cross reactivity between Widal test and anti-helicobactr pylori IgM.

Ceftriaxone lead to insignificant effects in reduction of anti-helicobacter IgM, but it lower anti-salmonella IgM that distinguished via Widal test significantly, therefore it not attenuate or prevents Widal test cross reactivity with anti-helicobacter pylori IgM.

What's more, ceftriaxone did not affects antibodies productions or cell mediated immunity [23], but other studies showed that ceftriaxone lead to noteworthy IgM production and inhibition of T- lymphocyte production and activation, this effects only appeared at higher doses (3g/day), this immunosuppressant effects emerge after seven days [24], but this not discovered in the present study may be due to small dose that unable for creation the suppressant effects or due to small sample size used in this study.

Additionally, Dalhoff 2005 study demonstrated that ceftriaxone but not cefotaxime inhibit angiogenic effects during acute immune response, ampiciline and most other B- lactam ring antibiotics lead to T-lymphocyte activation thus, the immunomodulator effects of B-lactam antibiotics were independent on B-lactam ring so it related to chemical structure of antibiotic [25].

Therefore, azithromycin and ciprofloxacin but not ceftriaxone attenuates antibody productions that determined by direct haemagglutination test leading to inhibition of cross reactivity with anti-helicobacter pylori antibodies.

In Widal test using cut-off 1/200 for O antigen, give 52% sensitivity and 88% specificity with 76% positive predictive value and 71% negative predictive value, the significance effects augmented when the diagnostic titer increase up to 92%, O titer sensitivity was 70%, but H titer was 30% in specificity of Widal test for typhoid fever diagnosis [26], but in the present study the cut-off value was 1/80 for O antigen.

False negative Widal test may be due to using immunosuppressant antibiotics while false positive widal test 6-8% may be due to cross reactivity with other bacterial types that independent on O or H antigens as in malaria [27], bladder carcinoma immunotherapy by intravesical Bacillus Calmet-Guerin which lead to high titer of IgM that cross react with the Widal test [28].

Helicobacter pylori infection causes significant immune reaction attended by an elevation of specific anti-helicobacter pylori with 95-100% specificity and 45% sensitivity, but this specific antibodies mostly IgM only present in 27% of helicobacter pylori infection, accordingly, ELISA- rapid test for anti-helicobacter pylori antibodies is less sensitive but more specific also, this test remain positive several months after eradication of helicobacter pylori infection by antimicrobial therapy so cannot differentiated between acute or chronic helicobacter pylori infection [29, 30], therefore, this test dose not cross react with Widal test but the reverse is true.

Furthermore, Karakus and Salih 2011 study revealed that cross reactivity between typhoid fever and helicobacter pylori infection may be mainly due to IgM induced via salmonella, but not by helicobacter pylori, thus false positive for helicobacter pylori infection is due to anti-

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salmonella IgM [30] which decreased by azithromycin and ciprofloxacin significantly and by ceftriaxone insignificantly.

Additionally, rapid decay in IgM against salmonella decrease cross reactivity with IgM against helicobacter pylori, Escherichia coli, and Yersinia enterocolitica, consequently IgM in salmonella agglutination test was implicated in this cross reactivity [31].

Moreover, McNulty et al 2011 study demonstrated that anti-helicobacter IgM give 20% cross reactivity with other bacteria that causes gastroenteritis mainly Yersinia entrocolitica and Escherichia coli but very minor cross reactivity with Salmonella typhi and paratyphi[32], this explained the attenuation effects of cross reactivity when typhoid fever treated with azithromycin or ciprofloxacin, thus Widal test cross reactivity is the foundation in the interpretations the false positive anti-helicobacter pylori IgM that can be modulated via azithromycin, ciprofloxacin and ceftriaxone.

6. Conclusion

Azithromycin, ciprofloxacin and ceftriaxone modulates and attenuate Widal test cross reactivity with anti-helicobacter pylori IgM.

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Competing of Interest

None

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