Jordan Journal of Pharmaceutical Sciences, Volume 2, No. 1, 2009

The Effect of COX1 and COX2 Inhibitors on the Antibacterial Activity of Selected Antibiotics against Standard and Methicillin- Resistant *Staphylococcus aureus*

Rula M. Darwish[1✉], T. Aburjai[2], S. Al-Khalil[2] and K. Hadidi[3]

[1] Department. of Pharmaceutics and Pharmaceutical Technology, Faculty of Phamacy, University of Jordan.
[2] Department. of Pharmaceutical Sciences, Faculty of Pharmacy, University of Jordan.
[3] Department. of Pathology, Microbiology and Forensic Medicine, Faculty of Medicine, , University of Jordan.

ABSTRACT

The antibacterial activity of combinations of COX1 or COX2 inhibitors and selected antibiotics, on methicillin resistance and standard strains of *Staphylococcus aureus* were assessed. Standardized serial dilution and viable counting methods were performed to evaluate the in vitro activity of seven different antibiotics and nine COX inhibitors. Common results between the two strains showed that the activity of gentamicin and chloramphenicol was improved by the use of COX1 and COX2 inhibitors, whereas nalidixic acid activity was not, when combined with both COX1 and COX2 inhibitors. The results showed that COX1 and COX2 inhibitors, except for celecoxib and rofecoxib, improved the activity of the antibiotics tested. Overall, the results suggest that COX inhibitors and antibiotics can be used advantageously together to improve the efficiency of antibioticsTaking into consideration the side effects of both drugs in the combinationfurther investigation might lead to use lower concentrations of antibiotics without compromising their effect, thus reducing the toxicity of these drugs.

Keywords: *S. aureus*, COX1 inhibitors, COX2 inhibitors, Antibiotic

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed drugs worldwide for rheumatic illnesses. NSAIDs exert their actions primarily by inhibiting the production of prostaglandins (PGs). There are two genes that express two similar but distinct isoforms of the enzyme cyclo-oxygenase (COX-1 and COX-2), the key enzyme-catalyzing the biosynthesis of PGs[1].

Both COX-1 and COX-2 are inhibited to varying degrees by all currently available (conventional) NSAIDs. Studies published so far support the hypothesis that the undesirable side effects of NSAIDs such as gastric erosion and renal dysfunctions are due to the inhibition of COX-1, while the anti-inflammatory effects are due to the inhibition of COX-2 [2]. However, cardiovascular events have recently been reported in studies on rofecoxib [3]. The inhibitory effects on COX-2-catalyzed prostaglandin biosynthesis of 49 plant metabolites were studied[4, 5]. These studies showed that phenolic compounds, eugenol, pyrogalol and cinnamaldehyde were found to inhibit COX-2. The inhibitors of COX-2 were investigated for the treatment of several inflammatory conditions such as rheumatoid arthritis, osteoarthritis, pain relief, prevention and migraine[6]. Recently, COX-2 has attracted attention because of its involvement in cancers [6, 7, 8].

In general, the 1st generation of NSAIDs (aspirin,

Received on 27/7/2008 and Accepted for Publication on 6/10/2008.
✉ E-mail: rulad@ju.edu.jo

indomethacin, ibuprofen, etc.) have comparable efficacy but different safety profiles probably due to differences in their ability to inhibit COX-1 at therapeutic doses [9]. The fact that COX-2 was found to be strongly associated with inflammation, and COX-1 was found to be responsible for maintaining physiological processes, was the starting point in search for specific COX-2 inhibitors. There are currently many selective COX-2 inhibitors in the market and under development by different pharmaceutical companies. These 2nd generation NSAIDs represent a new class of drugs (truly selective COX-2 inhibitors) and are considered a major advance in the management of pain and inflammatory diseases. Of these drugs, celecoxib SC-58635 or Celebra by Searle is the first to pass through the FDA advisory panel and now is approved for use in rheumatoid and osteoarthritis. Celecoxib is 375 times more selective for COX-2 relative to COX-1 and, at therapeutic doses; its plasma concentration does not reach the level required for effective COX-1 inhibition. In clinical trials celecoxib showed effective anti-inflammatory activity with virtually no gastrointestinal adverse effects compared to placebo.[10, 11]

Although the underlying causes of rheumatic arthritis are not known, evidence in the literature show that antibiotics could be administered for rheumatoid arthritis [12-17.] The remarkable clinical and pathological similarities between certain infectious diseases in animals and those of some human rheumatic illnesses have encouraged the search for a microbial etiology for these syndromes. A long list of aerobic and anaerobic bacteria, several viruses and mycoplasma have been proposed as important in these illnesses. These microorganisms can produce a variety of effects on host cells and tissue[13-25]. However, there were no indications in the literature to the antimicrobial activity of COX-2 or their interactions with the antibiotics. Our previous studies on the combination of certain antibiotics with different Jordanian plant extracts revealed that the resistance of *Staphylococcus aureus* and *Pseudomonas aeruginosa* can be reversed by some of these combinations. Moreover, some combinations showed better activity on both species as compared to each antibiotic alone [26, 27]. Our study therefore, is concerned with the in vitro possible effect of COX inhibitors on the antibacterial activity of selected antibiotics. *S. aureus* was chosen as a representative microorganism as it is known to be one of the important microorganisms in infections [28.]

MATERIALS AND METHODS

Microorganisms

Methicillin-resistant strains of *Staphylococcus aureus* (MRSA) was isolated from hospitalized patients from the Jordan University Hospital and approved by biochemical tests. Standard bacterial strains of *S. aureus* ATCC 25923 was also used as control.

Microorganisms were grown overnight at 37^0C on Mueller Hinton (MH) medium. Organisms were harvested, washed twice with peptone water, containing (gl^{-1}) peptone, 1; NaCL, 5; pH 7.2, and diluted to contain the required number of colony forming units ml^{-1} (cfu ml^{-1}).

Antibiotics

The following antibiotics were used in this study: Penicillin G (Merck), Gentamicin, Cefalexin (Hikma Pharmaceutical Manufacture Co.,Jordan), Tetracycline, Erythromycin (Arab Pharmaceutical Manufacture Co., Jordan), Nalidixic acid and Chloramphenicol (Fluka). The concentrations in the final plates for these antibiotics were equivalent to half their minimum inhibitory concentrations (MICs) (Table 1).

Table (1): Final concentrations of antibiotics in the (MH) agar plate (µg /ml)

Antibiotic	Final Concentration (½ MIC) µg ml^{-1}
penicillin G	2
chloramphenicol	12.5
gentamicin	3

Antibiotic	Final Concentration (½ MIC) µg ml^{-1}
cephalexin	16
erythromycin	8
tetracycline	8
nalidixic acid	4

COX inhibitors

Meloxicam (Arab Pharmaceutical Manufacture Co., Jordan), Diclofenac Na (Dar Al Dawa Co., Jordan), Diclofenac K (Tabouk Pharmaceutical MFG.Co, Tabouk Saudi Arabia), Mefenamic acid (Advanced Pharmaceutical Industry, Jordan), Aspirin, Naproxen (Arab Pharmaceutical Manufacture Co., Jordan) Celecoxib (Cearle, Augusta Ga, USA) and Rofecoxib (Merck). The concentrations used of these drugs (88µg ml^{-1}) were chosen to have no antibacterial activity when these drugs are used alone.

Determination of the Minimum inhibitory concentrations in vitro

Minimum inhibitory concentrations (MICs) of the antibiotics were determined experimentally and were in agreement with data published by the Committee for Clinical Laboratory Standards [29]. The concentrations of antibiotic used in the experiment were half the MIC so as to have no antibiotic effect of the on their own. Antibiotics were dissolved in DMSO solutions to give half the MIC in the final mixture (Table1). Preliminary results showed that DMSO solutions of these concentrations of antibiotics did not inhibit the growth of the microorganisms. At these concentrations, DMSO solutions of antibiotics were mixed with (MH) media and microorganisms as a control. COX inhibitors were added to give concentrations of 88µg ml^{-1} in the final mixtures. Preliminary experiments showed that these concentrations did not have antibacterial activity when these drugs are used alone . The bacterial suspension was added to give inoculum size of 10^4 cells in the final mixture of the COX inhibitors, the antibiotic and the (MH) media. The final mixture was mixed thoroughly, poured in a plate and then incubated at 37^0C for 24hrs. Control plates containing the COX inhibitors alone in the (MH) agar with the microorganisms were also included. The blank plates were prepared by mixing the solvent (DMSO) with (MH) agar and microorganisms. Preliminary experiments showed that the solvent did not exhibit any antimicrobial activity at the used concentration. The experiments were carried out in duplicate three times and correlated for the blank plates.

Calculation of % growth

After incubation period, the number of colonies on each plate was determined and correlated with the number of colonies on the corresponding blank plate. The number of colonies on each tested plate was expressed as percentage growth to the blank plate (growth on the blank plate was considered as 100%).

Statistical Analysis

All the results were obtained from triplicate experiments and the average of three trials were taken. Student's t-test was used . A significant level of 0.05 was applied.

Results

Table (2) and (3) show the effect of COX inhibitors combined with various antibiotics on the growth of methicillin-resistant and standard strains of *S. aureus*, respectively.

Table (2): The effect of COX inhibitors combined with various antibiotics on the growth of resistant *S. aureus*

No.	Cox inhibitors	%Growth on Combination with antibiotic* (± SE)**								
		**** Control	*** Blank	PEN. G	CHL	GEN	ERY	TET	NAL	Ceph
1	Meloxicam	100	100	83 ± 1.5	0^	3.2 ^ ± 0.7	0^	0^	68 ± 3.9	67.5 ± 3.3
2	Diclofenac Na	100	100	0^	0^	0^	0^	2.1^ ± 0.2	10.8^ ± 8.1	70 ± 6.6
3	Diclofenac K	100	100	0^	<1 ^	0^	5.1^ ± 6.8	0^	9.16^ ± 3.8	90 ± 14.9
4	Ibuprofen	100	100	88.5 ± 6.7	2.4^ ± 0.3	<1^	88 ± 5.2	0^	60.8 ± 4.6	121.2 ± 1.2
5	Mefenamic acid	100	100	39.2 ±2.2	1.5^ ± 0.8	0^	73.8 ± 6.9	0^	51.5 ± 4.6	53.4 ± 3.9
6	Aspirin	100	100	31.6 ± 6.2	0^	67.5 ± 3.5	2.7^ ± 6.5	0^	64.1 ± 4.2	76.6 ± 7.1
7	Naproxen	100	100	78.1 ± 5.9	2.7^ ± 0.2	<1^	39.5 ± 5.3	2.1^ ± .09	122.2 ± 8.3	107.3 ± 12.1
8	Celecoxib	100	100	100 ± 8.8	100 ± 6.8	100 ± 5.2	100 ± 6.3	100 ± 4.6	100 ± 4.8	100 ± 7.3
9	Rofecoxib	100	100	100 ± 5.8	100 ± 4.1	100 ± 4.5	100 ± 2.8	100 ± 5.1	100 ± 6.8	100 ± 3.9

* Penicillin G (Pen. G), Chloramphenicol (Chl), Gentamycin (Gent), Cephalexin (Ceph), Erythromycin (Eryth), Tetracycline (Tet) and Nalidixic acid (Nal).

** SE standard error of three different replicates.

***Blank plates were prepared by mixing the solvent with nutrient agar and microorganisms.

****Control plates contain the plant sample alone in nutrient agar with the microorganism .

^ statistically significant at the level of 0.05.

Results in tables (2) and (3) revealed that most COX inhibitors used have significant effect on improving the inhibitory effects of certain antibiotics on both resistant and standard *S. aureus*.

Table (3): The effect of COX inhibitors combined with various antibiotics on the growth of standard *S. aureus*

No.	Cox inhibitors	%Growth on Combination with antibiotic* (± SE)**								
		**** Control	*** Blank	PEN G	CHL	GEN	ERY	TET	NAL	Ceph
1	Meloxicam	100	100	0.16^ ± 1.5	0^	1.25^ ± 0.7	0^	75.8 ± 0.0	68 ± 3.9	67.5 ± 3.3
2	Diclofenac Na.	100	100	0^	0^	0^	0^	0^	6.5^ ± 8.1	10^ ± 6.6
3	Diclofenac K	100	100	65 ± 7.6	0^	0^	0.16^ ± 6.8	0^	8.2^ ± 3.8	6.6^ ± 4.9
4	Ibuprofen	100	100	0.75 ^ ± 6.7	0.16^ ± 0.3	6.5^ ± 3.0	0.45^ ± 2.3	0^	83.3 ± 4.6	61.6 ± 11.2
5	Mefenamic acid	100	100	30 ±1.5	1.5^ ±0.8	0^	69.5 ± 5.2	0^	49.1 ± 3.5	50 ± 2.5
6	Aspirin	100	100	1.25^ ±1.8	0^	14.6^ ± 4.2	0^	0^	72.5 ± 7.2	75 ±5.6
7	Naproxen	100	100	0.6^ ± 5.9	0^	0.83 ^ ± 4.4	17.5^ ± 5.3	0^	73.3 ± 8.3	33.3 ± 12.1
8	Celecoxib	100	100	100 ± 6.4	100 ± 6.2	100 ± 4.7	100 ± 6.2	100 ± 7.1	100 ± 5.0	100 ± 5.1
9	Rofecoxib	100	100	100 ± 4.8	100 ± 5.7	100 ± 4.6	100 ± 4.8	100 ± 4.2	100 ± 3.9	100 ± 5.3

* Penicillin G (Pen. G), Chloramphenicol (Chl), Gentamycin (Gent), Cephalexin (Ceph), Erythromycin (Eryth), Tetracycline (Tet) and Nalidixic acid (Nal).

** SE standard error of three different replicates.

***Blank plates were prepared by mixing the solvent with nutrient agar and microorganisms

****Control plates contain the plant sample alone in nutrient agar with the microorganism

^ statistically significant at the level of 0.05

This effect is obvious when COX inhibitors were combined particularly with chloramphenicol (Figure 1), gentamicin (Figure 2), erythromycin and tetracycline.

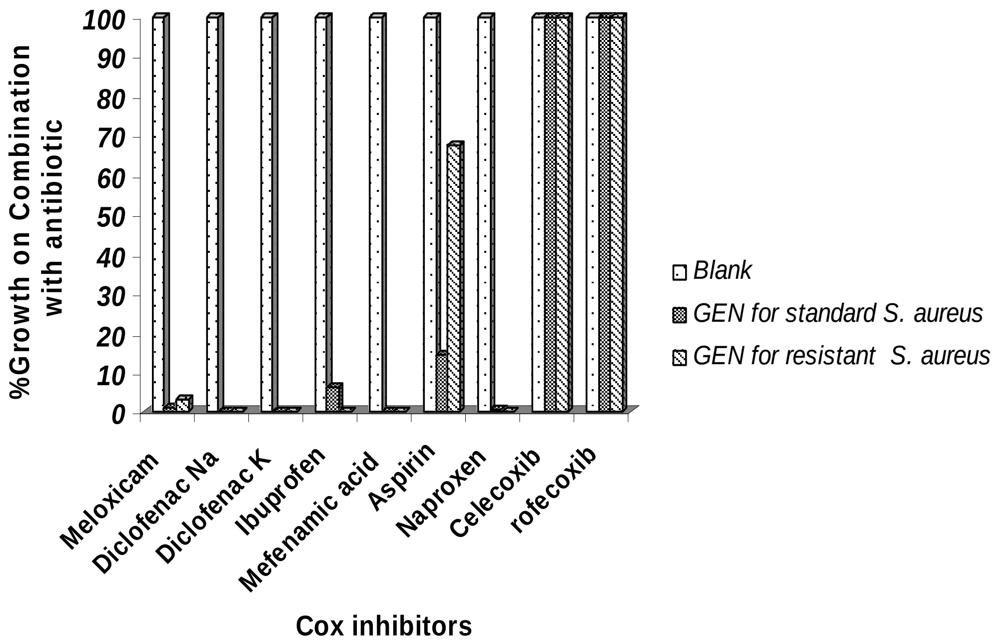

Figure (1): The effect of chloramphenicol and combinations of chloramphenicol with COX inhibitors on % growth of both standard and resistant *Staph. aureus*

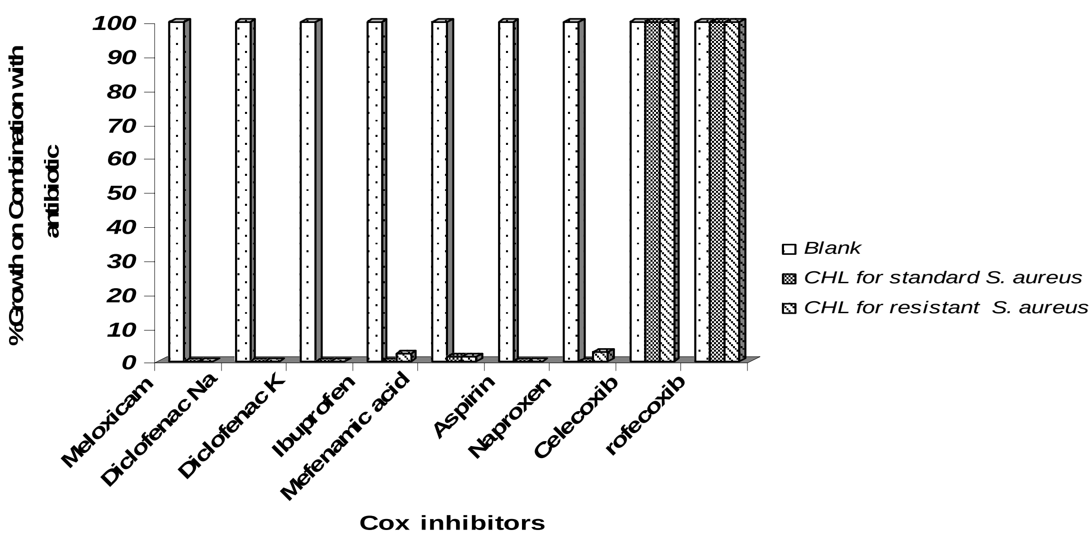

Figure (2): The effect of gentamicin and combinations of gentamicin with COX inhibitors on % growth of both standard and resistant *Staph. aureus*

On the contrary, no inhibition effect was noticed when these antibiotics were combined with celecoxib and rofecoxib. It is noteworthy that nalidixic acid combinations with COX inhibitors gave less inhibition in the % growth on both strains as compared with the combinations with other antibiotics used in this study.

The results also showed that combinations of antibiotics with diclofenac (sodium or potassium salts) gave the highest inhibition of % growth on both strains used even when combined with nalidixic acid (Tables 2 and 3).

DISCUSSION

Increasing amounts of clinical data support the role of microorganisms in arthritis [18,22-25]. These may draw more attention towards the use of antibiotics in arthritis therapy[15, 16]. Antibiotics might also be used for the treatment of different infections during the use of COX inhibitors in some patients.

The present study was carried out to screen the effect of the COX inhibitors in combination with the antibiotics to identify systems, which could be used advantageously to improve the efficacy of both drugs. The combination may also lead to use less concentrations of both drugs thus reducing the adverse effects of both drugs especially the antibiotics.

The representative bacterial species used in this study is a methicillin-resistant *S. aureus*, which is known to be one of the common causes of nosocomial infections. [28] The antibiotics used in this study were chosen to represent almost different groups of antibiotics. Their concentrations were chosen to be approximately half their MIC to guarantee that the effect produced is due to the combination and not to the effect of the antibiotic alone.

Our preliminary results showed that saturated solutions of the COX inhibitors in the absence of different antibiotics gave different levels of inhibition depending on the COX inhibitor used. For example, aspirin, sodium diclofenac, potassium diclofenac and naproxen have good antibacterial activity against standard strain of *S. aureus* while other COX inhibitors used showed very slight inhibition activity the inhibition effect of aspirin, sodium diclofenac, potassium diclofenac and naproxen is probably due to the chemical structure of these agents as carboxylic acids which affect cytoplasmic membrane permeability. None of the COX inhibitors used showed effect on resistant strains. However, the COX inhibitor concentrations used in combination with the antibiotics were chosen to have no antibacterial effect on their own against either the standard or the resistant stains. Concentrations of, COX inhibitors used (88µg ml^{-1}) allowed full growth of microorganisms. At those conditions COX inhibitors improved the inhibitory effects of some antibiotics against both resistant and sensitive *S. aureus*. This effect was significant ($p< 0.05$) when COX inhibitors, except celecoxib and rofecoxib, were combined with chloramphenicol, gentamicin, erythromycin and tetracycline (Table 2 and 3). Most NSAIDs in clinical use belong to the aryl-acetic and -propionic acid class. The effect seen is probably due to the effect of the COX inhibitors on the cytoplasmic membrane which lead to accumulation of inhibitory concentrations of the antibiotics at the target sites or due to the additional inhibitory effect of the COX inhibitor. [30] However, further studies are needed to confirm this assumption.

Combinations of celecoxib and rofecoxib solutions with all the antibiotics used did not improve the antimicrobial activity. Combination with the COX inhibitors (except for celecoxib, rofecoxib and naproxen) improved nalidixic acid activity, with significant improvement ($p< 0.05$) when sodium and potassium diclofenac were used. This may probably be due to the ability of COX inhibitor to improve the entrance of nalidixic acid through the cytoplasmic membrane and thus improved its activity. Further investigations are necessary to verify this point.

Combinations of cephalexin with the COX inhibitors showed significant improvement ($p< 0.05$) in its antimicrobial activity against the standard strain with the exception of celecoxib and rofecoxib as shown in Table (3). Cephalexin activity against resistant strain was slightly improved when combined with COX inhibitors except with ibuprofen, naproxen, celecoxib and rofecoxib

(Table 2). This indicates that there are some variations between resistant and standard strains. Further investigations have to be done to verify this point. Combinations of erythromycin with COX inhibitors showed significant improvement ($p < 0.05$) on its antimicrobial activity against the standard and resistant strain with the exception of celecoxib and rofecoxib for both strains, and ibuprofen for the resistant one.

On the basis of the experimental evidence obtained from this study, some general conclusions are presented as to the effect of the COX inhibitors on the activity of the antibiotics used. Celecoxib and rofecoxib did not improve the activity of the antibiotics. However, they did not decrease antibiotic activity at the concentration used against both resistant and sensitive strains of *S. aureus*. This might reflect the differences in chemical structure between these two selective COX2 inhibitors and the other NSAIDs used. This may lead to suggest that celecoxib and rofecoxib could be used with the antibiotics tested without interfering with their antibacterial activity. Having said that, one must point out those recent studies on rofecoxib that showed serious side effects of this COX inhibitor and recommended its withdrawal from the market.

The other COX inhibitors tested could be used to improve the efficacy of the antibiotics. It is noteworthy to mention that the effect of these antibiotics on the activity of COX inhibitors is worth to be studied to see if any of these antibiotics could possibly affect COX inhibition activity. This will contribute to increase the general knowledge of the effect of the promising combinations suggested earlier**.** Further studies are also needed to study the effect of other antibiotics which are used to treat Staphyloccocal infections such as flucloxacillin and vancomycin.

ACKNOWLEDGEMENT

The authors are grateful to the Deanship of Scientific Research, University of Jordan, Amman, Jordan, for their financial support of this work. Thanks to Mr. Amid Al-Taher, Mr. Ra'ed Abu Fares and Ahmad Mahasneh for their technical assistance. Thanks also to Hikma Pharmaceutical Manufacture and The Arab Pharmaceutical Manufacture for their supply of the Antibiotics.

REFERENCES

(1) Vane, J.R., Bakhle, Y.S. & Botting, R.M. Cyclooxygenases 1 and 2. *Annu Rev Pharmacol Toxicol* 1998; 38: 97-120.

(2) Bjorkman, D.J. The effect of aspirin and nonsteroidal anti-inflammatory drugs on prostaglandins. *Am J Med* 1998; 27B, 8S-12S.

(3) Mukherjee D., Nissen S. and Topol E. J. Risk of Cardiovascular Events Associated With Selective COX-2 Inhibitors. *J Am Med Assoc* .2001; 286:954-959.

(4) Ringbom, T., Huss U., Stenholm, A. et al. COX-2 inhibitory Effects of Naturally Occurring and Modified Fatty Acids. *J Nat Prod* 2001; 64(6): 745-749.

(5) Huss, U., Ringbom, T., Perera, P. et al.. Screening of Ubiquitous plant constituents for COX-2 inhibition with a scintillation proximity Based assay. *J Nat Prod* 2002; 65 (11): 1517- 1521.

(6) Nageswara Rao R., Meena S. and Raghuram Rao A. An overview of the recent developments in analytical methodologies for determination of COX-2 inhibitors in bulk drugs, pharmaceuticals and biological matrices. *J Pharm Biomed anal* 2005;39: 349-363.

(7) Koki, A.T. and Masferrer, J.L. Celecoxib: a specific COX-2 inhibitor with anticancer properties. *Cancer Cont.* 2002; 9: 28-35.

(8) Ermert, L., Dierkes, C. and Ermert, M. Immunohistochemical expression of cyclooxygenase isoenzymes and downstream enzymes in human lung tumors *Clin Cancer Res* 2003; 9: 1604-1610.

(9) Cryer, B. & Feldman, M.. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. *Am J Med* 1998; 104: 413-21

(10) Kawamori, T., Rao, C.V, Seibert, K., et. al Chemopreventive activity of celecoxib, a specific cyclooxygenase-2 inhibitor against colon carcinogenesis. *Cancer Res*, 1998; 58:3: 409-412

(11) Simon, L.S., Lanza, F.L.,Lipsky, P. et al. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor: efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. *Arth Rheumatol* 1998; 41 :(9), 1591-1602

(12) Greenwald ,R.A., Golub, L.M. , Lavietes, B, Ramamurthy, N.S. , Gruber, B., Laskin, R.S., Mc Namara,T.F. Tetracyclines Inhibits Human Synovial Collagenase in vivo and in vivo. *J Rheumatol*, 1987;14:1, and 28-32.

(13) Kloppenburg, M., Breedveld, F.C., Mitenburg, A.M.M., Dijkmans, BAC Antibiotics as disease modifiers in arthritis. *Clin Exp Rheumatol* 1993; 11 Suppl.8, S113-S115.

(14) Brandt, K.D. Modification by oral doxycycline administration of articular cartilage breakdown in osteoarthritis. *J Rheumatol* 1995; Supp43, 149-151.

(15) Tilley, B.C., Alarcon, G.S. and Heyse, S.P.. Minocycline in rheumatoid arthritis. A 48-week, double-blind, placebo-controlled trial. MIRA Trial Group. *Ann Intern Med* 1995; 122 :81-89.

(16) Trentham, D.E., Dysnesius Trentham, R.A. Antibiotic therapy for rheumatoid arthritis. Scientific and anecdotal appraisals. *Rheumatic Disease Clinics in North America* 1995; 21 : 817-834.

(17) Caruso, I. Twenty years of experience with intra articular rifamycin for chronic arthritis. *J International Med Res* 1997; 25 (6): 307-317.

(18) Midtvedt, T. Intestinal bacteria and rheumatic disease. *Scand J Rheumatol* 1987; 64 Suppl., 49-54.

(19) Fox, R.I., Luppi, M., Pisa, P. et al. Potential role of Epstein-Barr virus in Sjogren's syndrome and rheumatoid arthritis . *J Rheumatol* 1992;.32 Suppl., 18-24.

(20) Furr, P.M., Taylor-Robinson, D. & Webster, A.D.B. Mycoplasmas and ureaplasmas in patients with hypogammaglobulinemia and their role in arthritis: microbiological observation over twenty years. *Ann Rheum Dis* 1994; 53:183-187.

(21) Tsai, Y.T., Chiang, B.L., Kao, Y.F. et al. Detection of Epstein-Barr virus and cytomegalovirus genome in white blood cells from patients with juvenile rheumatoid arthritis and childhood lupus erythematosus. *Int Arch Allergy Immunol* 1995;106: 235-240.

(22) Aoki, S., Yoshikawa, K., Yokoyama, T. et al. Role of enteric bacteria in the pathogenesis of rheumatoid arthritis: evidence for antibodies to enterobacterial common antigens in rheumatoid sera and synovial fluids. *Ann Rheum Dis*1996; 55:363-369.

(23) Krause, A., Karadt, T. & Burmester, G.R.. Potential infectious agents in the induction of arthritis. *Curr Opin Rheumatol* 1996; 8:203-209

(24) Stephenson, J. Studies suggest a darker side of 'benign' microbes. *J the Am Med Assoc* 1997; 278:2051-2052.

(25) Haier, J., Nasralla, M., Franco, A.R. et al. Detection of mycoplasmal infections in blood of patients with rheumatoid arthritis. *Br J Rheumatol* 1999; 38:504-509.

(26) Aburjai, T., Darwish, Rula M., Al-Khalil, S., Mahafzah, A., and Al-Abbadi, A. Screening of antibiotic resistance inhibitors from local plant material against two different strains of *Pseudomonas aeruginosa*. *J.Ethnopharmacol* 2001; 76:39-44.

(27) Darwish, Rula M., Aburjai, T., Al-Khalil, S., Mahafzah, A. Screening of antibiotic resistance inhibitors from local plant material against two different strains of *Staphylococcus aureus*. *J Ethnopharmacol* 2002;79, 359-364

(28) Hugo, W.B. and Russell, A.D. *Pharmaceutical Microbiology* fifth edition, Blackwell Science London, UK. 1995.

(29) Committee for Clinical Laboratory Standards. 1984. M2-A3. In: Performance Standards for Antimicrobial Disk Susceptibility Tests, 3rd pp. 369-402.

(30) Bayly, C.I., Black, W.C., Loger, S. et al. Structure-based design of COX selectivity into flurbiprofen. *Bioorg Med Chem Lett*. 1999; 9: 307.

تأثير مثبطات COX1 و COX2 على مجموعة مختار من المضادات الحيوية على المكورات العنقودية الحساسة والمقاومة للمثيسيلين

رولا درويش[1]، طلال أبو رجيع[2]، سليمان الخليل[2] وكمال الحديدي[3]

[1] قسم الصيدلانيات والتقنية الصيدلانية، كلية الصيدلة، الجامعة الأردنية.
[2] قسم العلوم الصيدلانية، كلية الصيدلة، الجامعة الأردنية.
[3] قسم علم الأمراض، كلية الطب، الجامعة الأردنية.

ملخـص

هدفت هذه الدراسة إلى استيضاح اثر جمع مجموعه من المضادات الحيوية المختلفة مع بعض مثبطات COX-2, COX-1 في الزجاج على المكورات العنقودية الحسا سه أو المقاومة للمثيسيلين.

تمت دراسة سبعة أنواع من المضادات الحيوية و تسعة مثبطات لـ COX. أوضحت النتائج أن الجمع ما بين هذه المضادات الحيوية و مثبطات COX يؤثر في بعض الحالات على قدرة المضاد الحيوي لقتل الجراثيم العنقودية الحساسة أو المقاومة للمثيسيلين.

أظهرت النتائج أن قدرة الجنتامايسين والكلورامفنكول على مقاومه البكتيريا سواء الحساسة أو المقاومة قد ازدادت عند إعطاء مثبطات COX في نفس الوقت بينما لم تظهر التجارب نتائج مشابهة عند استعمال Nalidixic Acid.

من جهة أخرى أوضحت النتائج أن اغلب مثبطات COX-1, COX-2 و التي جمعت مع المضادات الحيوية الأخرى والتي استعملت في هذه التجربة قد أدت إلى تحسن ملحوظ في فعالية المضاد الحيوي بشكل عام ما عدا المثبطات Rofecoxib , Celecoxib.

بالخلاصة أظهرت نتائج هذه الدر اسه أن إعطاء المضادات الحيوية و التي استعملت في الدر اسه مع مثبطات COX في نفس الوقت يؤدي إلى تحسن فعالية المضاد الحيوي مما يشجع على إجراء مزيد من البحث في المستقبل للاستفادة من هذه النتائج في تقليل تركيز المضاد الحيوي المعطى في نفس الوقت مع مثبطات COX لتقليل آثارها الجانبية.

الكلمـات الدالـة: المكورات العنقودية، مثبطات COX1، مثبطات COX2، مضادات حيوية.

تاريخ استلام البحث 2008/7/27 وتاريخ قبوله 2008/10/6.