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# Drug-drug interaction may explain failed antibiotic effectiveness - an *in vivo* study

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**Abstract**
Non-steroidal anti-inflammatory drugs (NSAIDs) are often co-administered with antibiotics such as Ciprofloxacin, a second generation fluoroquinolone, in situations in which *Staphylococcus aureus* infections are accompanied with pain and inflammation. The contra- indications have not been found to attract deliberate study. This study was therefore to investigate possible interactions in co -administration of ciprofloxacin and some NSAIDs. The *in vivo* effect of co-administration of the NSAIDs (acetyl salicylic acid (ASA), piroxicam, indomethacin and paracetamol) with ciprofloxacin against *Staphylococcus aureus* in Swiss mice, rendered neutropenic by pre-treatment with cyclophosphamide, was evaluated using animal model. Using the murine thigh model, aliquots of the infected, homogenised thigh muscle were plated out in duplicate plates and incubated at 37°C. Growth of *Staphylococcus aureus* was observed and number of colony, forming units noted. All information obtained were recorded and analysed by standard statistical methods. Values of $p < 0.05$ were taken as significant. Co-administration of the NSAIDs with ciprofloxacin significantly reduced the number of CFU of Staphylococcus *aureus* in the order ASA > Indomethacin > Piroxicam > Paracetamol *(52* cfu; 47 cfu; 8 cfu; and 5 cfu) respectively. The four NSAIDs significantly exhibited varying degrees of inhibitory effect on *Staphylococcus aureus*, when compared with organism alone in broth, yielding 33 cfu; 25 cfu; 11 cfu; and 3 cfu, for ASA, Indomethacin, Piroxicam and Paracetamol, respectively when introduced without ciprofloxacin ($p<0.001$). These results demonstrate that these NSAIDs when co-administered with ciprofloxacin produce significant reduction in its antibacterial effect.

*Keywords*: *In vivo;* Ciprofloxacin; NSAIDs

## INTRODUCTION

Aspirin, indomethacin, piroxicam, and paracetamol are non- steroidal anti-inflammatory drugs (NSAIDs) which are indicated for relief of rheumatoid arthritis, osteoarthritis and bone pains, (Gotzsche 1989). The prominent NSAIDs include aspirin (acetyl salicylic acid), piroxicam, Indomethacin, Diflunsal, mafenamic acid and paracetamol. The NSAIDs have similar characteristics and tolerability. Aspirin has in addition antiplatelet effect by inhibiting the production of thromboxane. At low doses, it is used as long term to prevent heart attack, strokes and blood clot formation in people at high risk of developing cardiovascular diseases (Lewis *et al*., 1983). It may be given immediately after a heart attack or the death of cardiac tissue (Julian *et al.*, 1996). Indomethacin is used in the treatment of persistent ductus arteriosus in infants, premature retinopathy and all forms of arthritis and inflammatory disease (Sehar and Corrif, 2008) in the management of premature

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labour and in the prevention of amniotic fluid in polyhydramnious (Giles and Bisits).

Piroxicam, an oxicam class of NSAIDs, is indicated in similar settings as indomethacin. Paracetamol is a widely used over the counter analgesic and antipyretic commonly used for the relief of headaches and other minor aches and pains, the main mechanism of paracetamol activity is by inhibition of cyclooxygenase (COX)-2 (Hinz *et al*., 2008). The NSAIDs act as non-selective inhibitors of COX 1 and COX-2 which catalyse the formation of prostaglandin and thromboxane from arachidonic acid.

Ciprofloxacin is a proto-type second generation quinolone used worldwide. The prolific development of quinolones began in 1962, when Lescher *et al*. made the accidental discovery of nalidixic acid as a by-product of the synthesis of the antimalarial compound, chloroquine (Lescher *et al.*, 1962). This discovery led to the development of a large number of quinolone compounds, especially the newer quinolones in clinical use including ciprofloxacin (Andriole1994). The addition of specifically selected substituents at the key positions on the quinolone nucleus at different times made it possible to target specific groups of bacteria and improve on the pharmacokinetics of the earlier quinolone compounds, (Domagala 1994), (Gootz and Bugifly 1996) (Zhao *et al.*, 1997). The addition of a cyclopropyl group at the position N-1 yielded Ciprofloxacin, which has increased antibacterial activity against aerobic Gram- positive and Gram- negative pathogen (Crumplin and Smith 1976). It is noted for interaction with a very wide range of drugs including those used for treating seizures e.g. phenytoin sodium, inflammations (NSAIDs) antihypertensive, anticoagulants, vitamins, antacids, and a range of food supplements including iron, zinc, and magnesium (Ament *et al.*, 2000). Resistance to the quinolone is achieved by alterations in the outer membrane, diminishing the uptake of the drug or activation of an efflux pump that removes the quinolone before intracellular concentration is sufficient for inhibiting DNA metabolism (Acred, 1986). The resistance of many Gram negative bacteria and staphylococci to various quinolones is by this mechanism. The second mechanism is by changes in DNA gyrase subunits leading to decreased ability of the quinolones to bind this enzyme and thus interfere with DNA processes (Acred 1986).

Antibiotics and antibacterials including ciprofloxacin are used indiscriminately with or without prescription. Many people who have infections of the upper respiratory tract, urinary tract and open wounds, use ciprofloxacin bought over the counter before going to see a clinician. In most cases this antibiotic is taken concomitantly with vitamins, analgesics, antipyretics, some traditional medications, and other medications. Anecdotal reports indicate that often, microscopy, culture and sensitivity tests of *Staphylococcus aureus* isolates from most of these disease conditions still present results indicating sensitivity to the same organisms which did not respond *in vivo*.

It is likely therefore that a poorly understood phenomenon, probably drug-drug interaction may be responsible for the apparent failed *in vivo* action of the antibacterial. In situations where an individual patient has multiple system disease, for example an elderly man with chronic osteo-arthritis and recurrent UTI, requiring the use of ciprofloxacin and an NSAID, an insight into the possible interaction of ciprofloxacin and the NSAIDs could explain the treatment failures. From the available literature, there is yet no report of these possible interactions. This study was therefore aimed at evaluating the possible *in vivo* effects of co-administration of these NSAIDs (acetylsalicylic acid, piroxicam, indomethacin and paracetamol) with ciprofloxacin on the antibacterial activity of ciprofloxacin in

*Staphylococcus aureus*-induced infection in mice.

## EXPERIMENTAL

The in vivo experiments were carried out as follows:

**Preparation of drugs.** The concentrations of drugs in all the in vivo experiments were prepared as extrapolations from standard human clinical doses. For acetyl salicylic acid, a man of an average weight of 70 kg takes a maximum of 600 mg, while for piroxicam it is 20 mg, for indomethacin it is 50 mg while paracetamol is 1g maximum, ciprofloxacin is 500 mg-1g maximum and for cyclophosphamide, 150 mg/kg.

***In vivo* experiments.** The *work* was carried out based on animal model experiments. The animal models of Craig and Andes, 2002, and Acred 1986 were modified for these experiments. Using the standard method described by Craig and Andes neutropenia was achieved by two separate injections of cyclophosphamide given as 150 mg/kg, 4 days and 100 mg/kg, one day before infection with *Staphylococcus aureus.* Thigh infections were produced by injection of 0.1 m l of over-night culture of *Staphylococcus aureus* into the right hind thigh. Sixty-six sets of experiments (including the control groups), involving four drugs and one hundred and sixty- two mice of both sexes weighing between 18g and 36 g were used.

**Control experiments.** Three mice were used for this experiment: one was rendered neutropenic by pre -treatment with cyclophosphamide and so was labelled immune compromised (ICd); one not treated with cyclophosphamide and was labelled immune competent (IC) had the right hind limb shaved and infected by inoculation with 0.1 ml of $10^8$dilution of overnight culture of *Staphylococcus aureus* in Muller Hinton (MH) broth. The third mouse was IC had its right thigh shaved but was not infected with *Staphylococcus aureus* and served as control. Immediately after infection with *Staphylococcus aureus*, the three mice were humanely sacrificed, their right hind limbs were disinfected with 70 % ethanol, aseptically severed, weighed, homogenised with 10 ml sterile ¼ strength Ringer´s solution.0.1 ml of the homogenates were pippeted one after the other and doubly diluted to obtain $10^6$ dilution from which 0.2 ml was pippeted into 18.8 ml molten MSA at 43$^o$C, thoroughly mixed and plated out in duplicates in sterile Petri dishes. The set agar plates were incubated at 37$^o$C for 24 hours and were observed for growth *of Staphylococcus aureus* and recorded.

**In vivo effects of co-administration of ciprofloxacin and NSAIDs.** *In vivo* effect of co-administration of ciprofloxacin and acetyl salicylic acid (ASA), indomethacin, piroxicam and paracetamol on the antibacterial activity of ciprofloxacin against *Staphylococcus aureus* in cyclophosphamide untreated and pre- treated mice. Twenty-seven mice were randomly allocated into four groups (A, B, C, and D). Three of These groups, (A, B, C) had eight mice each, while the fourth group, (D) had three mice.

The group D was the control- group for this experimental group. The three mice in this group were treated as in the Control experiment above.

Groups A, B and C were divided into two sets; one set that received cyclophosphamide referred to hereafter as ICd and those that did not receive cyclophosphamide referred to as IC. The groups A, B, C, represent the eight experiments recorded at the $6^{th}$, $12^{th}$ and $24^{th}$ hours respectively. These experiments are represented as follows:

Three untreated mice (IC) had their right hind limb thighs shaved and inoculated with 0.1 ml of $10^6$ dilution of an overnight culture of *Staphylococcus aureus.* At six-hour intervals ($6^{th}$, $12^{th}$, $24^{th}$) they were humanely sacrificed, their right hind limb disinfected,

and aseptically severed, weighed, and homogenised with 10 ml of sterile ¼-strength Ringers solution. 0.1 ml of the homogenates were pippeted one after the other and ten-fold diluted to obtain $10^6$ dilution from which 0.2 ml was pippeted into 18.8 ml molten MSA at 43$^o$C, thoroughly mixed and plated out in duplicates in sterile Petri dishes. The set agar plates were incubated at 37$^o$C for 24 hours and were observed for growth *of Staphylococcus aureus* and recorded.

Three mice pre-treated with cyclophosphamide (ICd) (150 mg/kg, and100 mg/kg) had the thigh of their right hind limb shaved 24 h later, disinfected with 70% ethanol and inoculated with 0.1 ml of $10^6$ dilution of an overnight culture of *Staphylococcus aureus.* At six-hour intervals ($6^{th}$, $12^{th}$, $24^{th}$) they were humanely sacrificed, their right hind limb disinfected, and aseptically severed, weighed, and homogenised with 10mls of sterile ¼-strength Ringers solution. 0.1 ml of the homogenates was treated as in Experiment 1 and the plates were observed for growth *of Staphylococcus aureus* and recorded.

Three mice pre-treated (ICd) with cyclophosphamide (150 mg/kg, and100 mg/kg) had the thigh of their right hind limb shaved 24 hours later, disinfected with 70 % ethanol and inoculated with 0.1 ml with of $10^6$ dilution of an overnight culture of *Staphylococcus aureus* and injected with ciprofloxacin 14.29 mg/kg IP two hours post-infection with *Staphylococcus aureus.* At six-hour intervals ($6^{th}$, $12^{th}$, $24^{th}$) they were humanely sacrificed their right hind limb disinfected, and aseptically severed, weighed, and homogenised with 10 ml of sterile ¼-strength Ringers solution. 0.1 ml of the homogenates was treated as in Experiment 1 and the plates were observed for growth *of Staphylococcus aureus* and recorded.

The procedure above was repeated using three mice which were not pre-treated with cyclophosphamide. Three mice pre-treated (ICd) with cyclophosphamide (150 mg/kg, and100 mg/kg) had the thigh of their right hind limb shaved 24 hours later, disinfected with 70 % ethanol and injected with 0.1 ml of $10^6$ dilution of an overnight culture of *Staphylococcus aureus* and injected with Ciprofloxacin 14.29 mg/kg concomitantly with acetyl salicylic acid (8.57 mg/kg) intraperitoneally (IP) and orally (po) respectively two hours post-infection with *Staphylococcus aureus* At six hours intervals ($6^{th}$, 12th, and $24^{th}$) they were humanely sacrificed their right hind limb disinfected, and aseptically severed, weighed, and homogenised with 10 ml of sterile ¼-strength Ringers solution. 0.1 ml of the homogenates was treated as in Experiment 1 and the plates were observed for growth *of Staphylococcus aureus* and recorded.

The procedure above was repeated using three mice which were not pre-treated with cyclophosphamide. Three mice pre-treated (ICd) with cyclophosphamide (150 mg/kg, and100 mg/kg) had the thigh of their right hind limb shaved, disinfected with 70 % ethanol and injected with 0.1 ml of $10^6$ dilution of an overnight culture of *Staphylococcus aureus* injected intraperitonealy (ip) with acetyl salicylic acid (8.57 mg/kg) orally two hours post-infection with *Staphylococcus aureus.* At six-hour intervals ($6^{th}$, 12th, and $24^{th}$) they were humanely sacrificed their right hind limb disinfected, and aseptically severed, weighed, and homogenised with 10 ml of sterile ¼-strength Ringers solution. 0.1 ml of the homogenates was treated as in Experiment 1 and the plates were observed for growth *of Staphylococcus aureus* and recorded.

The procedure above was repeated using three mice which were not pre-treated with cyclophosphamide.

This same procedure was strictly followed in determining the *in vivo* effect of co-administration of ciprofloxacin and Indomethacin (Indo)Po, Piroxicam(po),

piroxicam (ip), paracetamol (po), and paracetamol (ip)against *Staphylococcus aureus* in cyclophosphamide-untreated and pre-treated mice. All data obtained were tabulated and were fed into the computer and analysed by using SPSS Version 16. Inferential statistics involved the use of Student t-test and one-way analysis of Variance (ANOVA). Values of $p<0.05$ were regarded as significant.

## RESULTS

Fig. 1 to Fig. 7 demonstrated the results of the 8 *in vivo* experiments: Fig 1. demonstrated the *in vivo* effect of ciprofloxacin in the presence of acetylsalicylic acid on the growth of *staphylococcus aureus* in cyclophosphamide pre-treated and untreated mice.

Fig.2. demonstrated the *in vivo* effect of ciprofloxacin in the presence of indomethacin on the growth of *staphylococcus aureus* in cyclophosphamide untreated and pre-treated mice.

Fig 3. *In vivo* effect of ciprofloxacin in the presence of piroxicam (ip) on the growth of *Staphylococcus* in cyclophosphamide untreated and pre-treated mice.

Fig 4 demonstrated the *in vivo* effect of ciprofloxacin in the presence of piroxicam (po) on the growth of *staphylococcus aureus* in cyclophosphamide pre-treated and untreated mice

Fig 5 demonstrated the *in vivo* effect of ciprofloxacin in the presence of piroxicam (po) on the growth of *staphylococcus aureus* in cyclophosphamide pre-treated and untreated mice.

Fig. 6 demostrated the *in vivo* effect of ciprofloxacin in the presence of paracetamol (po) on the growth of *Staphylococcus aureus* in cyclophosphamide untreated and pre-treated mice.

In all the figures, there was minimal growth of organism in the control experiment (Group 0) which did not differ significantly from one another.

Experiment 1 in each of the series demonstrated that the untreated, hence IC animals showed mild growth of organism by the $6^{th}$ hour with little or no difference in the number of colony-forming units between $6^{th}$ and the 24th hour.

In all the series of experiment 2, ICd (pre-treated with cyclophosphamide) without ciprofloxacin or NSAID, demonstrated significant growth of the organism when compared with the growth of organism in experiment 1 ($p<0.001$).

In the experiment 3 series, introduction of ciprofloxacin into the ICd showed a significant reduction in the number of colony-forming units across the series ($p< 0.001$). In experiment 4, the introduction of ciprofloxacin into the IC (untreated with cyclophosphamide) also showed a significant reduction in the number of colony-forming units across the series. ($p< 0.001$).

In the experiment 5 series, ICd (animal + cyclophosphamide + organism +ciprofloxacin+ NSAID), there was significant growth in the ASA groups ($p<0.001$) and also in the indomethacin group ($p< 0.001$) but to a much reduced extent in the piroxicam and paracetamol groups.

In experiment 6 series, IC (animal No cyclophosphamide +organism + ciprofloxacin + NSAID), ASA showed luxuriant and significant growth of the organism with more colony-forming units ($p<0.001$) than the other NSAIDs.

In the experiment 7 series, ICd (animal + cyclophosphamide + organism +NSAID), the ASA group followed by the Indomethacin group showed more significant growth than piroxicam and paracetamol.

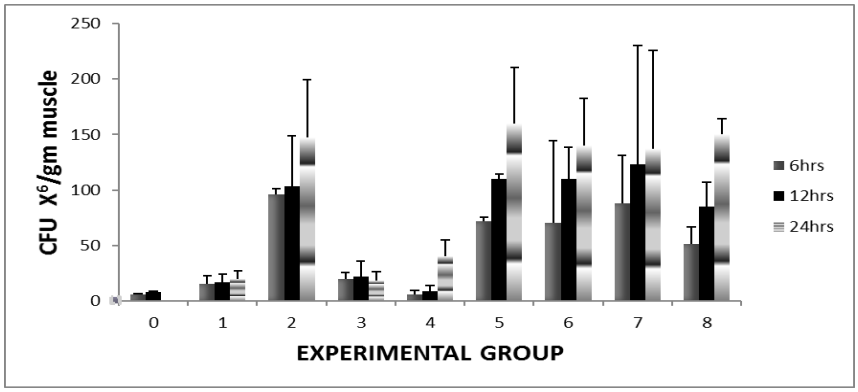


**Fig1.** *In vivo* effect of ciprofloxacin in the presence of acetylsalicylic acid on the growth of *staphylococcus aureus* in cyclophosphamide pre-treated and untreated mice (values are given as Mean ±SEM)
ANIMAL ONLY; ANIM+ORG; ANIM+CYCLO+ORG:
0 = CONTROL 1 = ANIM+ORG; 2 = ANIM+CYCLO+ORG; 3 = ANIM+CYCLO+ORG+CIP ; 4 = ANIM+ ORG +CIP; 5 =ANIM+CYCLO+ORG +CIP+IASA; 6 = ANIM +ORG+CIP+ASA; 7 = ANIM+CYCLO+ORG+ASA; 8 = ANIM+ORG+ASA. $p \geq 0.001$ n=5

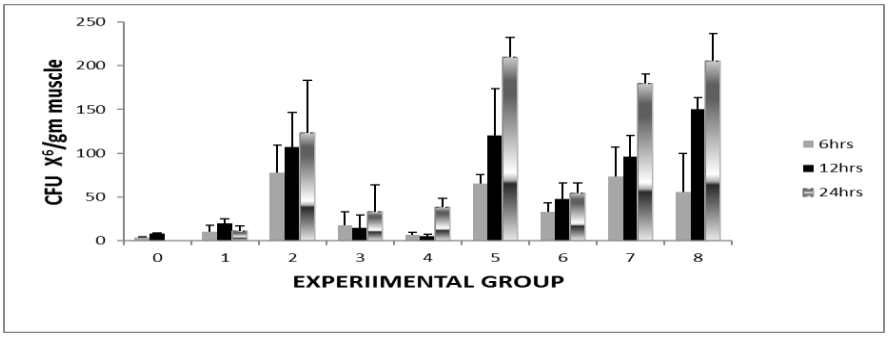


**Fig.2.** *In vivo* effect of ciprofloxacin in the presence of indomethacin on the growth of *staphylococcus aureus* in cyclophosphamide untreated and pre-treated mice (values are given as Mean ±SEM).
ANIMAL ONLY: ANIM+ORG: ANIM +CYCLO+ORG:
0 = CONTROL 1=ANIM+ORG; 2= ANIM+CYCLO+ORG; 3=ANIM+CYCLO+ORG+CIP ; 4= ANIM+ ORG +CIP; 5 =ANIM+CYCLO+ORG +CIP+INDO; 6= ANIM +ORG+CIP+INDO; 7=ANIM+CYCLO+ORG+INDO; 8 =ANIM+ORG+INDO. P<0.001 n=5

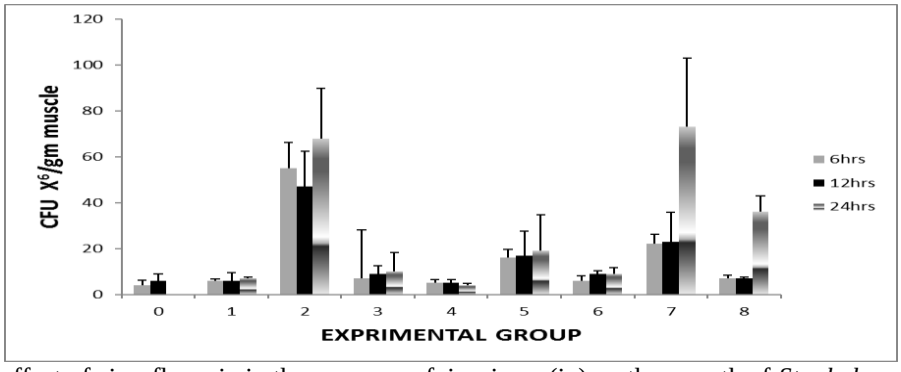


**Fig 3.** *In vivo* effect of ciprofloxacin in the presence ofpiroxicam (ip) on the growth of *Staphylococcus aureus* in cyclophosphamide untreated and pre-treated mice (Values are given as Mean ±SEM).
ANIMAL ONLY: ANIM+ORG; ANIM+CYCLO+ORG:
0 = CONTROL 1 = ANIM+ORG; 2 = ANIM+CYCLO+ORG; 3 = ANIM+CYCLO+ORG+CIP; 4 = ANIM+ ORG +CIP; 5 = ANIM+CYCLO+ORG +CIP+PIROX; 6= ANIM +ORG+CIP+PIROX; 7 = ANIM+CYCLO+ORG+PIROX; 8 = ANIM+ORG +PIROX. P<0.001 n=5

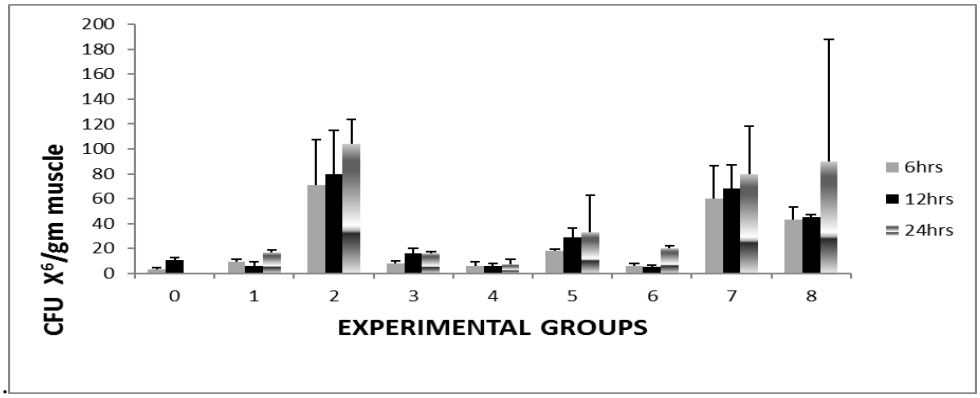


**Fig 4.** *In vivo* effect of ciprofloxacin in the presence of piroxicam (po) on the growth of *staphylococcus aureus* in cyclophosphamide pre-treated and untreated mice (values are given as Mean ±SEM)
ANIMAL ONLY: ANIM+ORG: ANIM+CYCLO+ORG:
0 = CONTROL: 1 = ANIM+ORG; 2 = ANIM+CYCLO+ORG; 3 = ANIM+CYCLO+ORG+CIP ; 4 = ANIM+ ORG +CIP; 5 = ANIM+CYCLO+ORG +CIP+PIROX; 6 = ANIM +ORG+CIP+PIROX; 7 = ANIM+CYCLO+ORG+PIROX; 8 = ANIM+ORG +PIROX. p≥ 0.001 n=5

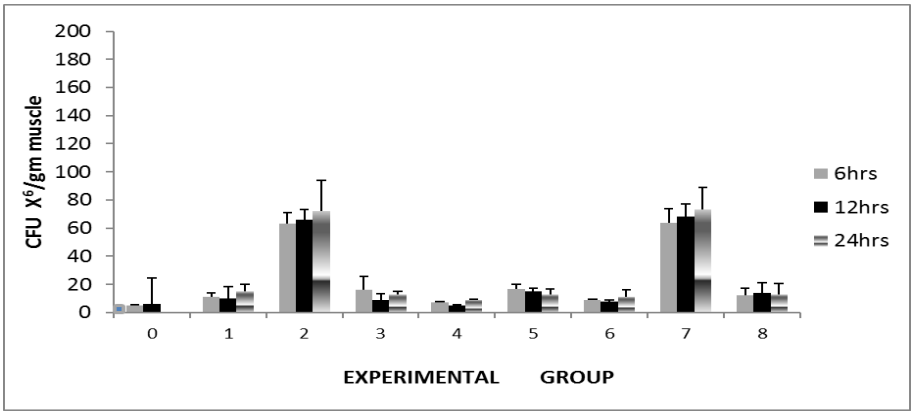


**Fig. 5.** *In vivo* effect of ciprofloxacin in the presence of paracetamol (ip) on the growth of *staphylococcus aureus* in cyclophosphamide pre-treated and untreated mice (values are given as Mean ±SEM).
ANIM ONLY: ANIM+ ORG: ANIM + CYCLO+ ORG:
0 = CONTROL; 1 = ANIM+ORG; 2 = ANIM+CYCLO+ORG; 3 = ANIM+CYCLO+ORG+CIP; 4 = ANIM+ ORG +CIP; 5 = ANIM+CYCLO+ORG +CIP+PCM; 6 = ANIM +ORG+CIP+PCM; 7 = ANIM+CYCLO+ORG+PCM; 8 = ANIM+ORG+PCM. p≥ 0.001 n=5

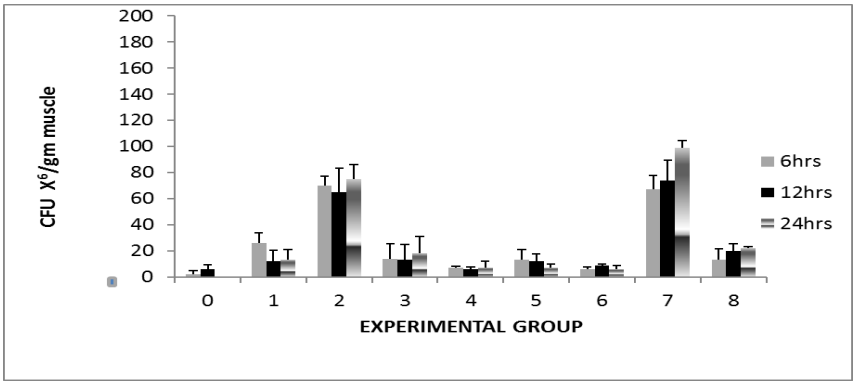


**Fig. 6.** *In vivo* effect of ciprofloxacin in the presence of paracetamol (po) on the growth of *Staphylococcus aureus* in cyclophosphamide untreated and pre-treated mice (values are given as ±SEM).
ANIM ONLY: ANIM+ ORG: ANIMAL + CYCLO+ ORG:

0 = CONTROL 1 = ANIM+ORG; 2 = ANIM+CYCLO+ORG; 3 = ANIM+CYCLO+ORG+CIP ; 4= ANIM+ ORG +CIP; 5 =ANIM+CYCLO+ORG +CIP+PCM; 6= ANIM +ORG+CIP+PCM; 7=ANIM+CYCLO+ORG+PCM; 8 =ANIM+ORG+PCM. $p \geq 0.001$ n=5

In the experiment 8 series, IC (animal + No cyclophosphamide + organism +NSAID), there was significant growth in the ASA group when compared with experiment 1 but not significant as in experiment 7. In the paracetamol group there was not much difference in growth between the series. In piroxicam (ip), there was also not much difference in growth between the series. In piroxicam (po), there was significant growth when compared with experiment 1. In piroxicam (ip) and paracetamol (ip) and (po) there was no significant growth when compared with experiment1. In the indomethacin group, there was significant growth, though not much lower than group 7, ($p<0.01$).

## DISCUSSION

The results of the *in vivo* experiments indicate that acetyl salicylic acid and ciprofloxacin co administration had greatest impairment effect on ciprofloxacin antibacterial activity thus resulting in greater number of colony-forming units of *Staphylococcus aureus*. This is followed closely by Indomethacin, then, piroxicam and paracetamol respectively in descending order of activity. The results of the *in vivo* experiments, clearly demonstrated marked increase in the number of cfu in the pre-treated mice which was a result of uninhibited growth of organisms alone. The introduction of ciprofloxacin in the pre-treated and untreated mice caused a marked reduction in the cfu as a result of uninhibited antibacterial effect of the ciprofloxacin against *Staphylococcus aureus* in the immune-competent and the immune–compromised animals respectively. The concomitant administration of NSAIDs with the ciprofloxacin caused increase in the number of cfu thereby reducing the antibacterial effect of ciprofloxacin.

Like acetyl salicylic acid, indomethacin, and piroxicam and to a lesser extent paracetamol each independently had varying degrees of inhibitory effect on the growth of *Staphylococcus aureus*. Shirring *et al.,* (2006) demonstrated antibacterial and bacteriostatic activity of some NSAIDS against *Helicobacter pylori* at therapeutically achievable doses. Such activity can explain the independent inhibitory effect of NSAIDs observed in this work on growth of the *Staphylococcus aureus* but cannot explain the degree of inhibition in the presence of ciprofloxacin, an effect which cannot be described as synergistic or additive. There has been no report in literature about the inhibitory effects of the other NSAIDS used in this work on ciprofloxacin. Of the three drugs employed in this study, only acetyl salicylic acid has been largely reported. Price *et al*. (2000), reviewed the effects salicylate has on various bacterial species on one hand, growth of certain bacteria in the presence of salicylate can induce an intrinsic multiple antibiotic resistant phenotype; on the other hand, growth in the presence of salicylate can reduce the resistance to some antibiotics and affect virulence factor production in some bacteria.

Gustafson *et al.* (1999) demonstrated in their in *vitro* work that growth of *Staphylococcus aureus* in the presence of salicylate induced resistance to strains susceptible to fluoroquinolone and increased resistance to fluoroquinolone in resistant strains. In their work however, salicylate was added to already grown cultures of *Staphylococcus aureus* resulting in what was described as many fold increase or decrease in growth with probable transformation of the organisms. In this in *vivo* study, salicylate (or

the other NSAID) was administered concomitantly with ciprofloxacin post infection with the *Staphylococcus aureus.* This allowed for a uniform interaction of the NSAID with both the ciprofloxacin and the organism. Moreover, the incubation here was for 24 hours only. Dorothy *et al.* (2012) identified and characterized the promoter and regulatory elements of Rv0560c induces antibiotic resistance and showed that promoter activity could also be induced by compounds structurally related to salicylate, such as aspirin or para-aminosalicylic acid.

There are two possible mechanisms for the interaction of the NSAIDs with ciprofloxacin: (a)The 4-keto-3carboxylic acid moiety of the fluoroquinolones constitutes the active site of the quinolones. Ionization of the fluoroquinolones by the loss of $H^+$ makes the molecule capable of interacting with any in-coming entity. Thus the NSAIDs may bind to this active site of the fluoroquinolone rendering it inactive and hence it cannot inactivate DNA gyrase and topoisomerase IV in the bacterium. (b) The NSAIDs are known to have low pKa (Julian *et al.,* 1996), (Sehar and Corrif, 2008), (Giles and Bisits), which may affect the physico-chemical nature of the fluoroquinolones (like the ionization state) which will affect its solubility and hence its bioavailability. Thus lethal concentration levels may not be attained.

There appear to be probably an unexplained pharmacodynamic interaction between ciprofloxacin and these NSAIDS which is responsible for the inhibition of the antibacterial activity of ciprofloxacin against *Staphylococcus aureus.* Therefore, concomitant use of these NSAIDs and ciprofloxacin in the treatment of diseases implicated in *Staphylococcus aureus* must be cautiously applied.

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