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Therapeutic Efficacy of Ofloxacin and Ornidazole vs Mebatic: Toxicity Profile and Antioxidant Defense Study

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Abstract: This study investigated to comapre the efficacy of ofloxacin, ornidazole and mebatic (Fixed dose combination ornidazole plus ofloxacin). Various parameters related to blood, liver and kidney were studied in the monotherapy as well as in the combination therapy. To further explore the mechanisms of better efficacy showed by combination, antioxidant defense status was also explored. The mice were fed standard pelleted diet and water *ad libitum*. The test room was air conditioned with temperature 22±2°C, humidity 60.5% and with artificial fluorescent light 10-12 h of light and dark, respectively. Twenty four mice were divided into four groups containing six mice in each group. Ofloxacin treated group recieved 3.3 mg kg^{-1} b.wt. day^{-1}, ornidazole treated group received 8.3 mg kg^{-1} b.wt. day^{-1} and mebatic treated group received 11.6 mg kg^{-1} b.wt. day^{-1} whereas control group received normal saline. The findings of present study suggested that the combination formulation showed no signs of toxicity when tested for liver and kidney related parameters. The combination formulation also attenuated the oxidative stress and also preserved the antioxidant enzyme levels (catalase and superoxide dismutase) in treated group. From the results of our study it can be concluded that the combination was safe as compared to treatment of the individual agents. It was also infer that the normalized antioxidant defense status might be responsible for decrease in hepatotoxicity and nephrotoxicity in the combination group as compared with monotherapies using either agent.

Key words: Oxidative stress, antioxidant enzymes, malonaldialdehyde, ofloxacin, ornidazole, mebatic

INTRODUCTION

Combination therapy with two or more agents having complementary mechanisms of action is such an innovation that has extended the range of options in the treatment of various human diseases (Khan *et al*., 2008). Fluoroquinolones (FQs) exhibit potent *in vitro* and *in vivo* antibacterial activities (Kurt *et al*., 2008). The fluoroquinolones and nitroimidazoles are currently enjoying extensive worldwide clinical applications because of their good bioavailability and pharmacokinetic profile. Due to the broad spectrum of activity of fluoroquinolones, it may be possible to exploit this drug as drug of choice against range of bacteria. Though, ofloxacin (the broad antibacterial spectrum of quinolones) having very high gram-negative activity, including moderate activity against *Pseudomonas aeruginosa* (Khan *et al*., 2008; Messadi *et al*., 2008), most anaerobic pathogens and several

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Gram-positive strains are moderately susceptible (Hamilton-Miller and Shah, 1997; Messadi *et al*., 2008). To increase the spectrum and to lessen the chances of resistance it was combined with ornidazole, a nitroimidazole. It has an antibacterial spectrum that includes most of anaerobes (Kumar *et al*., 2007b; Kurt *et al*., 2008) and its single-dose is an important alternative for the treatment of many conditions than other nitroimidazoles (Saracoglu *et al*., 1998). Apart from this both the drugs have similar pharmacokinetic profile with long half-lives suitable for parenteral administration (Michael *et al*., 1990; Ptitsina *et al*., 2007). All this ensures better patients compliance. The additive advantage over monotherapy is that both drugs act on DNA and provide sequential block on bacterial DNA to contribute to synergistic activity.

Oxidative stress is known to be involved in hepatotoxicity and nephrotoxicity of many antimicrobial agents. The reactive oxygen species stress generated in the body is well known for its malevolent attributes. Flouoroquinolones are well documented to cause oxidative stress (Bertino and Fish, 2000; Pouzaud *et al*., 2006). It has also been convicted with adverse effects associated with ofloxacin led to hepatotoxic and nephrotoxic manifestations (Lomaestro, 2000; Montagnac *et al*., 2005). Due to the generation of these notorious free radicals the class of flouroquinolones is also associated with retinopathy, a long term complication of diabetes.

To be effective as antibiotics not only should inhibit target microorganisms but also should not exert adverse effects on host organisms. Adverse reactions that might range from mild effects such as hypersensitivity, rashes and gastrointestinal intolerance to more serious complications such as toxicity to various organs which may lead to death due to organ failure. To achieve these aims, mebatic (ofloxacin plus ornidazole) was fabricated. This combination is superior in terms of potency and spectrum, but the safety profile is still an unexplored area. Therefore we evaluated the toxicity profile of the combination formulation on liver and kidney related parameters. Available reports suggest that the monotherapy with both agents caused mild to moderate toxicities in liver and kidney related parameters (Dharnidharka *et al*., 1998). Therefore, the aim of this study was to assess the corelation between oxidative stress and protection from hepatotoxicity and nephrotoxicity shown by the combination regimen that yielded beneficial attributes in terms of potency, spectrum as well as adverse effects.

MATERIALS AND METHODS

Study Conduct

The study was carried out from 15th December 2008 to 20th March 2009 in pre-clinical Unit of Venus Medicine Research Centre, Venus Remedies Ltd. Baddi (India).

Chemicals

All the chemicals used in the present study were procured from Sigma, St.Louis, MO, USA. Other chemicals of analytical grade were purchased locally. The antibiotics such as ofloxacin, ornidazole and mebatic were obtained from Venus Remedies Ltd. India. The ratio of fixed dose combination of ofloxacin-ornidazole and was 1: 2.5.

Experimental Animals and Treatments

Healthy *Mus musculus* mice (male mice, 15- 20 g weight) were divided into four groups (three treatment groups and one control group). Each group consists of 6 male animals. The mice were fed standard pelleted diet and water *ad libitum*. They were housed in polyurethane cages at controlled room temperature of 22±2°C and a relative humidity of 60.5%

and a constant light-dark schedule (10-12 h of light and dark, respectively). The study protocol was approved by Institutional Animal Ethics Committee. All four groups were assigned to respective treatments:

Control group (n = 6): Isotonic saline treated group
Ofloxacin treated group (n = 6): 3.3 mg kg^{-1} b.wt. day^{-1}
Ornidazole treated group (n = 6) : 8.3 mg kg^{-1} b.wt. day^{-1}
Mebatic treated group (n = 6): 11.6 mg kg^{-1} b.wt. day^{-1}

The doses employed were based upon the human dose after conversion to that of mice (Paget and Barnes, 1964). All drugs were administered intramuscularly for 7 days continuously. At the end of treatment (eighth day), blood samples were drawn in heparinized vials from the heart by cardiac puncture under the light ether anesthesia. The organs were quickly blotted, weighed on digital balance and processed for enzymatic evaluation. Oxidative stress parameters were evaluated in blood, liver and renal tissue.

Preparation of Homogenate

Liver and kidney (15%w/v) homogenates were prepared in phosphate buffer-KCl solution containing 0.15 mol L^{-1} KCl in 0.05 mol L^{-1} Na_2HPO_4-NaH_2PO_4 buffer, pH 6.8. The enzyme preparations were left for at least 1 h at 0-4°C. All the enzymes assays were carried out at 25°C.

Enzyme Assays

Superoxide Dismutase (SOD) Assay

The reaction mixture composed of 1.0 mL carbonate buffer (0.2 M, pH 10.2), 0.8 mL KCl (0.015 M), 100 µL of blood and water to make the final volume to 3.0 mL. The reaction was started by adding 0.2 mL of epinephrine (0.025 M). The change in absorbance was recorded at 480 nm at 15 sec interval for 1 min at 25°C. Blank was run simultaneously. One unit of enzyme activity is defined as the amount of enzyme causing 50% inhibition of auto oxidation of epinephrine (Misra and Fridovich, 1972).

Catalase Assay

The reaction mixture consisted of 0.3 mL phosphate buffer, (0.2 M pH 6.8), 0.1 mL H_2O_2 (1 M) and water to make the final volume to 3.0 mL. The reaction was started by adding the suitable aliquot of enzyme preparation. The change in the absorbance was recorded at 15 sec interval for 1 min at 240 nm at 25°C. Suitable control was run simultaneously. One unit of enzyme activity was defined as the amount of enzyme that liberates half of the peroxide oxygen from H_2O_2 in 100 sec at 25°C (Luck, 1957).

Measurement of Lipid Peroxidation

Free radical mediated damage was assessed by the measurement of the extent of lipid peroxidation in the term of malondialdehyde (MDA). It was determined by thiobarbituric acid reaction. The reaction mixture consisted of 100 µL of enzyme preparation, 0.20 mL of 8.1% Sodium Dodecyl Sulphate (SDS), 1.5 mL of 20% acetic acid (pH 3.5), 1.5 mL of 0.8% Thio Barbituric Acid (TBA) and water to make up the volume to 4.0 mL. The tubes were boiled in water bath at 95°C for 1 h and cooled immediately under running tap water. Added 1.0 mL of water and 5.0 mL of mixture of n-butanol and pyridine (15:1 v/v) and vortexed. The tubes were centrifuged at 3500 rpm for 30 min. The upper layer was aspirated out and optical density was measured at 532 nm. The reference standard used was 1,1, 3,3 tetraethoxypropane (Ohkawa *et al*., 1979).

Estimation of Creatinine Levels and Uric Acid

Creatinine levels were determined by the alkaline picrate method using diagnostic kits (Bayer Diagnostics India Ltd., Baroda, Gujrat India).

Estimation of Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase Activities (SGPT) Activity

The SGOT and SGPT is specific marker of liver toxicity. The SGOT levels were determined by using diagnostic kits (Bayer Diagnostics India Ltd., Baroda, Gujrat India).

Statistical Analysis

Results are expressed as Mean±SD. Significance of difference between groups was evaluated by using ANOVA. If ANOVA shows significant differences, post hoc analysis was performed using Tukey test. $p<0.05$ was considered as statistically significant.

RESULTS

A significant ($p<0.001$) decreased in SOD and catalase activities were found in blood, liver and renal tissues of ofloxacin and orinidazole groups as compared to control group. These activities were found to be increased significantly within 8 days in case of mebatic treated group ($p<0.001$) as compared to ofloxacin and orinidazole treated groups and become close to control group (Table 1-3).

A significant increased in MDA level was found in blood, liver and renal tissues ($p<0.001$) of ofloxacin and orinidazole groups as compared to control group. While in case of mebatic treated group, the MDA level was lowered significantly ($p<0.001$) within 8 days of treatment and almost come near to normal level when compared to control group (Table 1-3).

Table 1: Effect of ofloxacin, ornidazole and mebatic on biochemical parameters related to liver and kidney dysfunction as well as oxidative stress parameters in blood of mice

Parameters	Control	Ofloxacin	Orinidazole	Mebatic
	----------(n=6)----------			
SOD (unit mL^{-1})	1.96±0.04	1.60±0.26a	1.84±0.12a	1.90±0.18a
Catalase (unit mL^{-1})	172.59±1.59	132.00±1.29a	160.50±1.26a	192.00±0.82a
MDA (nmole mL^{-1})	1.45±0.16	2.30±0.18b	2.00±0.16b	1.40±0.14a
Uric acid (mg dL^{-1})	2.50±0.30	3.15±0.10b	3.03±0.20b	2.60±0.16a,c
Creatinine (mg dL^{-1})	0.78±0.12	2.03±0.11b	1.71±0.14b	0.85±0.10a,c
SGOT (IU L^{-1})	38.50±1.55	43.87±1.40a	43.00±1.29a	40.00±1.90a,c
SGPT (IU L^{-1})	40.00±1.39	44.00±1.39a	41.98±1.19a	41.00±1.60a,c

All results are expressed as Mean±SD; a = $p<0.001$(highly significant); b = $p<0.01$(significant); c = $p<0.05$ (not significant)

Table 2: Effect of ofloxacin, ornidazole as single agent and mebatic on biochemical parameters related to kidney dysfunction as well as oxidative stress parameters in renal tissue of mice

Parameters	Control	Ofloxacin	Ornidazole	Mebatic
	----------(n=6)----------			
SOD (unit mg^{-1} tissue)	1.80±0.22	1.20±0.13a	1.73±0.12a	1.82±0.17a
Catalase (unit g^{-1} tissue/min)	161.42±1.17	110.07±1.46a	133.45±1.48a	147.83±1.57a
MDA (nmol g^{-1} tissue)	1.00±0.45	1.60±0.13b	1.15±0.13b	0.93±0.12a
Uric acid (mg dL^{-1})	1.70±0.22	2.50±0.26b	2.12±0.20b	1.80±0.13a
Creatinine (mg dL^{-1})	0.80±0.18	1.80±0.22b	1.10±0.22b	1.00±0.18a

All Results are expressed as Mean±SD, a = $p<0.001$(highly significant); b = $p<0.01$(significant); c = $p<0.05$ (not significant)

Table 3: Effect of ofloxacin, ornidazole as single agent and mebatic on biochemical parameters related to liver dysfunction as well as oxidative stress parameters in liver tissue of mice

Parameters	Control	Ofloxacin	Ornidazole	Mebatic
	----------(n=6)----------			
SOD (unit mg^{-1} tissue)	1.60±0.10	1.20±0.31a	1.30±0.17a	1.57±0.19a
Catalase (unit g^{-1} tissue/min)	132.33±1.25	111.00±1.15a	119.50±0.96a	137.17±1.34a
MDA (nmol g^{-1} tissue)	1.40±0.04	2.00±0.13b	1.60±0.13b	1.20±0.06a
SGOT (IU L^{-1})	22.67±1.32	34.17±1.36a	31.00±1.39a	27.00±1.62a, c
SGPT (IU L^{-1})	26.68±0.98	41.27±1.12a	36.38±1.14a	24.00±1.34a,c

All Results are expressed as Mean±SD; a = $p<0.001$(highly significant); b = $p<0.01$(significant); c = $p<0.05$ (not significant)

Serum creatinine levels were significantly increased ($p<0.01$) in blood and renal tissues of ofloxacin and orinidazole groups as compared to control group. Serum creatinine level was significantly ($p<0.01$) decreased in mebatic treated group when compared to ofloxacin and orinidazole treated groups. No significant ($p<0.05$) change was observed in creatinine level of mebatic treated group compared to control group (Table 1, 2).

Uric acid and urea levels were increased significantly ($p<0.01$) in blood and renal tissues of ofloxacin and orinidazole groups as compared to control group. These levels were reduced significantly ($p<0.001$) within 8 days in case of mebatic treated group as compared ofloxacin and orinidazole treated groups and almost come near to normal level when compared to control group (Table 1, 2).

Serum Glutamyl Oxaloacetic Transaminase (SGOT) and Serum Glutamyl Pyruvic Transaminase (SGPT) level were significantly increased ($p<0.001$) in blood and liver tissues of ofloxacin and orinidazole groups as compared to control group respectively. Alternatively, in case of mebatic treated group, the level of SGOT and SGPT revert back significantly near to normal level ($p<0.05$) when compared to control group (Table 1, 3).

DISCUSSION

Ofloxacin is known to cause potentially serious, adverse effects involving organs like kidney and liver. Antimicrobials have long been known to cause various forms of nephrotoxicity occurring as allergic interstitial nephritis, granulomatous interstitial nephritis, necrotising vasculitis, allergic tubular nephritis or a tubular necrosis (Lomaestro, 2000; Montagnac *et al*., 2005). Apart from this fluroquinolones are also involved in serious hepatotoxic consequences (Clark *et al*., 2001). Present results showed that single therapy of ofloxacin and ornidazole increases hepatotoxicity and nepherotoxicity. Liver enzyme levels were evaluated and it was observed that SGPT and SGOT level was significantly increased as compared to control. Similarly, there was increase in the parameters related to kidney function such as creatinine and uric acid levels in ofloxacin treated animals. Present results stated that fixed dose combination of ofloxacin plus ornidazole i.e., mebatic is beneficial than individual therapy of ofloxacin and ornidazole.

Nitroimidazole derivatives are commonly used in the treatment of protozoal and anaerobic infections and few reports of their hepatotoxicity are available (Harputluoglu *et al*., 2007; Tabak *et al*., 2003). In this study, ornidazole slight increases the SGPT, SGOT, creatinine and uric acid level which are markers of liver and kidney dysfunction. In case of mebatic treated group all the rats comes near to control level indicating that mebatic is more beneficail than ofloxacin and ornidazole individually.

Dharnidharka *et al*. (1998) and Pouzaud *et al*. (2006) reported that cellular damage of liver and kidney is due to reactive oxygen species generated by fluroquinolones. It is well documented by various reports that most of antimicrobials cause nephrotoxicity and

hepatotoxicity by increasing oxidative stress (Chowdhury *et al*., 2006; Stratta *et al*., 1994). Oxidative stress diminishes the activity of endogenous antioxidant enzyme defense system (SOD and Catalase levels), which play a significant protective role. Oxidative stress exerts its devastating effects by directly damaging cellular proteins, lipids and DNA, or indirectly, by affecting normal cellular signaling and gene regulation and antioxidants have been reported to provide protection in various pathological conditions (Kumar *et al*., 2007a; Tikoo *et al*., 2008). Keeping these evidences in mind we evaluated the parameters of oxidative stress for each individual agent as well as for the combination group. Ofloxacin treatment confirmed oxidative stress mediated damage in kidney and liver as it showed increase in MDA level while decrease in SOD and Catalase activity in blood, kidney as well as liver tissue. This increase in MDA was not observed in mebatic treatment. The SOD and Catalase levels were also comparable to control which confirmed decrease in oxidative stress with the combination therapy.

In addition to kidney, liver blood was also evaluated for oxidative parameters. We observed increased levels of MDA the along with increase in creatinine and uric acid levels. The antioxidant enzyme levels were also depleted in the groups treated with single agents. The findings of present study suggested significant increase in oxidative stress. However in blood samples of animals in combination treated group no alteration was observed in any of the above mentioned parameters as compared to control. These results further approve biochemical safety profile of the combination regimen and reduction in oxidative stress.

In summary, this data suggest that mebatic is safe in terms of adverse effects. The mechanism for this protection was not very clear. One of the probable mechanisms for enhanced effects as well as better safety profile is the antioxidant potential of the fixed dose combination of ofloxacin-ornidazole combination. We have previously established beneficial effect of combination against gram-positive and anaerobic pathogens in various bacterial susceptibility tests.

It can be concluded that mebatic, a parenteral therapy consisting of quinolones together with imidazole derivative ornidazole as fixed dose combination showed antioxidant potential and offers no obvious toxicity as compared to individual drug treatment.

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