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Comparative Toxicity Profile Study of Mebatic vs. Ofloxacin, Ornidazole and Metronidazole Drugs in Rat Model

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Abstract: In the present study, the researchers have tried to determine the toxicity of a novel fixed dose combination of ofloxacin plus ornidazole (mebatic) vs. ofloxacin, ornidazole and metronidazole alone drugs in the plasma of Wister rats. Total thirty Wister rats were randomly selected and divided into five groups of six rats each. Group I was control normal saline (0.9% NaCl) treated group where as rest of four groups were treated with respective drugs. The drugs were given to animals intravenously for 24 days and blood samples were collected on 12th and 24th day after treatment for the measurement of biochemical parameters. Present results showed that there was insignificant increase in hemoglobin level on 12th and 24th day in mebatic treated group as compared with other treated groups. The levels of uric acid, alkaline phosphatase, creatinine, bilirubin and hepatic enzymes were found to be lowered but insignificant in mebatic treated group on 12th and 24th day treatment in comparison to ofloxacin, ornidazole as well as metronidazole alone treated groups. These levels were found to be almost near to normal level in mebatic treated group. When ofloxacin, ornidazole as well as metronidazole alone treated groups were compared to control group, these hepatic and renal parameters were significantly increased except in mebatic treated group. The level of free radical mediated damage was also significantly decreased in mebatic treated group in comparison to other treated groups. Therefore, these findings concluded that mebatic drug is less toxic and most effective than ofloxacin, ornidazole and metronidazole alone which improved hepatic and renal enzymes and free radical mediated damage.

Key words: Mebatic, ofloxacin, ornidazole, metronidazole, hepatic and renal enzymes

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). Mebatic is a novel fixed dose combination of ofloxacin plus ornidazole. Ofloxacin is a fluoroquinolone antibiotic considered to be a second-generation fluoroquinolone. Ornidazole is a nitroimidazole antiprotozoal agent used in *ameba* and *trichomonas* infections. The fluoroquinolones and nitroimidazoles are currently enjoying extensive worldwide clinical applications because of their good bio availability and pharmacokinetic profile. Due to the broad spectrum of activity of

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fluoroquinolones, it may be possible to exploit this drug as drug of choice against a wide range of bacteria. Though, ofloxacin (the broad antibacterial spectrum of quinolones) having very high gram-negative activity and moderate activity against *Pseudomonas aeruginosa* (Khan *et al*., 2008; Messadi *et al*., 2008), most anaerobic pathogens and several Gram-positive strains are moderately susceptible (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).

The reactive oxygen species generates stress in the body. It 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). Oxidative stress is known to be involved in hepatotoxicity and nephrotoxicity due to many antimicrobial agents. Several 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 present study was to monitor the toxicity in the term of oxidative stress as well as biochemical parameters in respective drugs treated groups.

MATERIALS AND METHODS

Study Conduct

The study was carried out in Preclinical Division of Venus Medicine Research Centre, Baddi, H.P. India from 25th October 2009 to 15th December 2009.

Chemicals

All of the biochemical reagents used in the present study were procured from Sigma, St. Louis, MO (USA). Other chemicals purchased locally were of analytical grade. All of the antibiotics such as ofloxacin, ornidazole, metronidazole and a fixed dose combination of ofloxacin plus ornidazole (mebatic) drugs were obtained from Venus Remedies Ltd. India.

Animals and Treatments

Total thirty Wister rats, (weighing 125 to 130 g) used in the experiment were housed at controlled temperature and humidity in an alternating 12 h light and dark cycle with free access to food and water. The study was approved by the institutional animal ethical committee. The drugs were given to animals intravenously according to their body weight for 24 days treatment. The rats were divided into five groups of six rats each as given below:

- **Group I:** Control normal saline treated group
- **Group II:** Ofloxacin treated group (3.33 mg kg^{-1} b.wt.)
- **Group III:** Ornidazole treated group (8.33 mg kg^{-1} b.wt.)
- **Group IV:** Mebatic treated group (11.66 mg kg^{-1} b.wt.)
- **Group V:** Metronidazole treated group (8.33 mg kg^{-1} b.wt.)

After administration of respective drugs for 24 days treatment according to their body weight, 2.0 mL blood sample was collected from retro-orbital sinus on 12th and 24th day

in (3.8%) sodium citrate containing polypropylene tubes and plasma was separated for estimation of biochemical parameters and oxidative stress parameters.

Plasma Preparation

Sodium citrate containing blood, 1.5 mL was centrifuged at 6600 rpm for 15 min at 2-4°C in cooling centrifuge and supernatant was carefully removed in other clean polypropylene tube for assay of hepatic and renal enzymes.

The rest part of blood sample was used for measurement of hemoglobin and malondialdehyde in all treated groups.

Estimation of Hemoglobin

The hemoglobin level was measured with Sahli hemoglobinometer.

Measurement of Malondialdehyde

It was determined by thiobarbituric acid reaction. The reaction mixture consisted of 200 μL of blood sample, 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).

Measurement of Creatinine

Creatinine level was determined by the alkaline picrate method using diagnostic kits (Bayer Diagnostics India Ltd., Baroda, Gujrat India). The level was analyzed according to the method of Henry *et al*. (1974).

Biochemical Parameters

All biochemical parameters such as uric acid, urea, bilirubin, alkaline phosphatase and hepatic enzymes (SGOT, SGPT) were estimated by using commercially available diagnostic kits (Bayer Diagnostics India Ltd, Baroda, Gujrat India).

Statistical Analysis

The data obtained was analyzed statistically. All values are expressed as Mean±SD. One-way Analysis of Variance (ANOVA) with student-Newman-Keuls comparison test was used to determine statistical difference between control vs. treated groups and with each other. The p-values <0.05 were considered statistically significant.

RESULTS AND DISCUSSION

After intravenous administration of combination drug (mebatic) as well as alone drugs for 24 days in each groups except control group, there was no mortality was seen until the completion of experiment.

Effect of Mebatic on Hemoglobin Level

There was insignificantly increased hemoglobin level in mebatic treated group as compared with control normal saline treated group but in case of ofloxacin, ornidazole as well

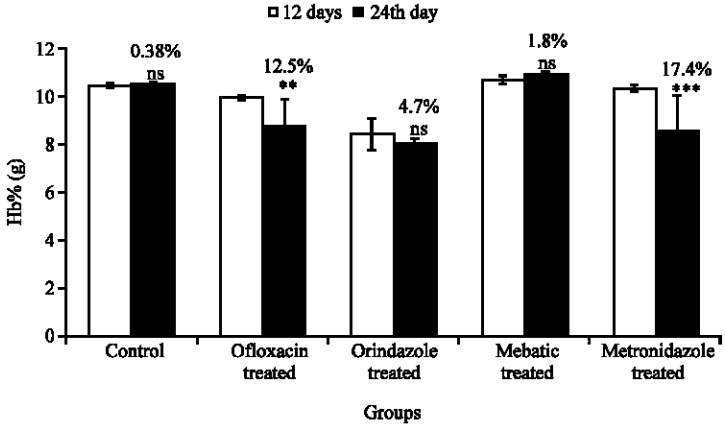

Fig. 1: Values are represented in Mean±SD. All the data were compared control vs. all treated groups and vs. each other. The statistical data were measured by Newman keul test. The percentage change was observed between 12th and 24th day. Toxicity study of Mebatic drug vs. Ofloxacin, Ornidazole and Metronidazole in hemoglobin level on 12th and 24th day. **p<0.01, ***p<0.001, ns: Not significant

as metronidazole alone treated group, the hemoglobin level was decreased. The hemoglobin level was found higher in mebatic treated group on 12th and 24th day in comparison to other treated group and almost near to control level. The level of hemoglobin was found to be lowered significantly (p<0.01; 12.5%) in ofloxacin treated group and (p<0.001; 17.4%) in metronidazole treated group on 24th day when compared with 12th day treatment (Fig. 1).

Effect of Mebatic on Urea Level

The urea level was slightly insignificantly increased in ofloxacin, metronidazole and mebatic treated group on 12th day as compared with control treated group. But in case of ornidazole treated group, this level was significantly higher as compared with all other respective treated drug groups. When this level was compared on 12th and 24th day in all treated groups, the level was found to be decreased (p<0.01; 18.68%) in mebatic treated group where as in all groups, there was a minor increase. In case of control group the level was unchanged on 12th and 24th day (Fig. 2).

Effect of Mebatic on Uric Acid and Alkaline Phosphatase Level

Uric acid was increased significantly (p<0.001;73.5%) in ofloxacin treated group but in case of ornidazole and metronidazole treated groups, the level of uric acid was insignificantly increased as compared with control normal saline treated group on 12th and 24th day. The level of uric acid was found lowered in mebatic treated group in comparison to all other treated group and almost near to control group on 12th and 24th day treatment. In case of alkaline phosphatase, the level was found to be higher and significantly increased in ofloxacin treated group (p<0.001;100%), ornidazole treated group (p<0.01;10.4%) as well as in metronidazole alone treated group (p<0.001;100.4%) on 12th and 24th days treatment. The level was increased in all treated groups except mebatic treated group on 12th and 24th day. The level was decreased 6.5% in mebatic treated group but did not altered very significantly and came almost near to control group (Fig. 3, 4).

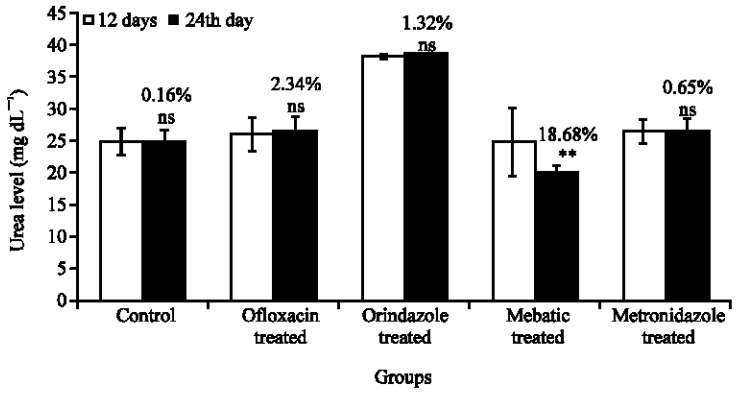

Fig. 2: Values are represented in Mean±SD. All the data were compared control vs. all treated groups and vs. each other. The statistical data were measured by Newman keul test. The percentage change was observed between 12th and 24th day. Toxicity study of Mebatic drug vs. Ofloxacin, Ornidazole and Metronidazole in urea level on 12th and 24th day. **p<0.01, ns: Not significant

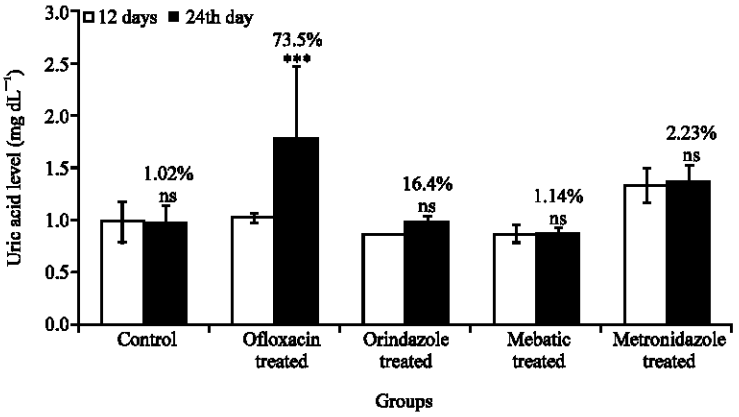

Fig. 3: Values are represented in Mean±SD. All the data were compared control vs. all treated groups and vs. each other. The statistical data were measured by Newman keul test. The percentage change was observed between 12th and 24th day. Toxicity study of Mebatic drug vs. Ofloxacin, Ornidazole and Metronidazole in uric acid level on 12th and 24th day. ***p<0.001, ns: Not significant

Effect of Mebatic on Creatinine Level

Creatinine level was significantly increased in ofloxacin and ornidazole treated group as compared with control group on 12th day treatment. But in case of mebatic and metronidazole treated groups, the level was slightly decreased. On 24th day, the level was significantly increased in ofloxacin, ornidazole as well as metronidazole alone treated groups as compared with control treated group. The level was found lowered in mebatic treated group when compared with control normal saline treated group. When compared between 12th and 24th day amongst all treated groups, the creatinine level was found be insignificantly higher in

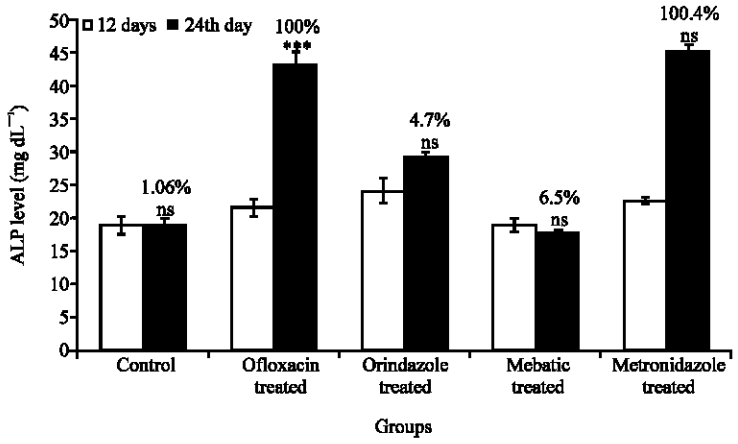

Fig. 4: Values are represented in Mean±SD. All the data were compared control vs. all treated groups and vs. each other. The statistical data were measured by Newman keul test. The percentage change was observed between 12th and 24th day. Toxicity study of Mebatic drug vs. Ofloxacin, Ornidazole and Metronidazole in ALP level on 12th and 24th day. **p<0.01, ***p<0.001, ns: Not significant

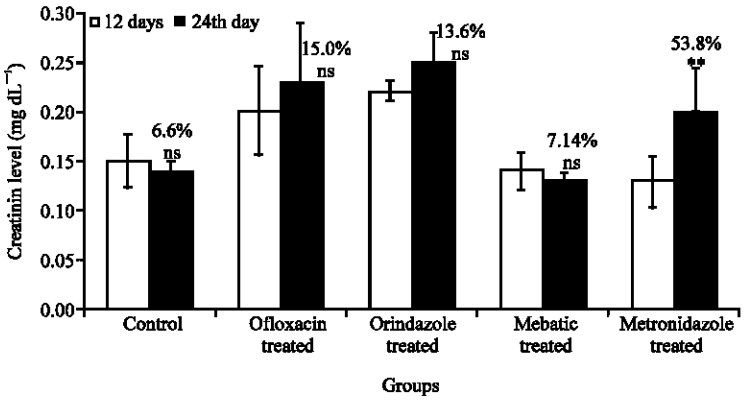

Fig. 5: Values are represented in Mean±SD. All data were compared control vs. all treated groups and vs. each other. The statistical data were measured by Newman keul test. The percentage change was observed between 12th and 24th day. Toxicity study of Mebatic drug vs. Ofloxacin, Ornidazole and Metronidazole in Creatinine level on 12th and 24th day. **p<0.01, ns: Not significant

ofloxacin (15%), ornidazole (13.6%) treated groups whereas in case of metronidazole treated group, the level was significantly elevated (p<0.01; 53.8%). The level was reduced 7.14% in mabetic treated group on 24th day when compared with 12th day treatment (Fig. 5).

Effect of Mebatic on Bilirubin Level

The bilirubin level was found to be increased in ofloxacin treated group as compared with control group on 12th day treatment. While in case of other treated groups, the level

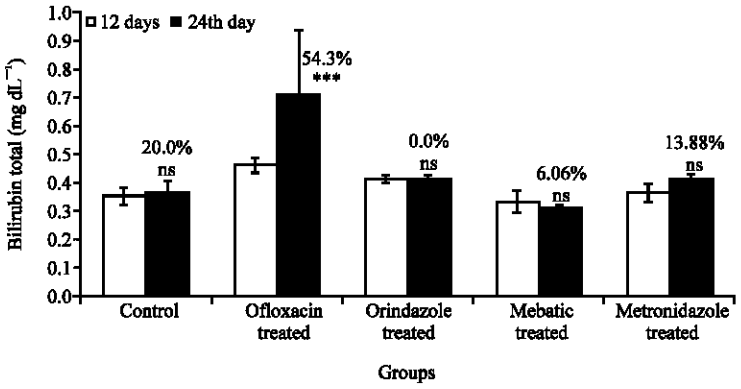

Fig. 6: Values are represented in Mean±SD. All the data were compared control vs. all treated groups and vs. each other. The statistical data were measured by Newman keul test. The percentage change was observed between 12th and 24th day. Toxicity study of Mebatic drug vs. Ofloxacin, Ornidazole and Metronidazole in Bilirubin level on 12th and 24th day. ***p<0.001, ns: Not significant

was not altered very significantly. In case of mebatic treated group, the level was minorly lowered as compared with control group on 12th day treatment. When all treated groups were compared on 12th and 24th day, the level was significantly higher ($p<0.001$; 54.3%) in ofloxacin treated group but the level was not altered in ornidazole treated group. The level of bilirubin was increased about 13.8% in metronidazole treated group on 24th day when compared with 12th day treatment. On comparative study between 12th and 24th day treatment, the level was reduced about 6.06% in mebatic treated group on 24th day (Fig. 6).

Effect of Mebatic on Hepatic Enzymes

Serum Glutamyl Oxaloacetic Transaminase (SGOT) level was significantly increased ($p<0.001$) in ofloxacin treated group as compared with control group as well as other treated groups. When these treated groups were compared to each other on 12th and 24th day, the SGOT level was significantly increased ($p<0.05$; 33.3%) in ornidazole treated group. While in case of other treated groups, the level of SGOT was decreased in mebatic treated group however, the level was insignificantly increased in ofloxacin and metronidazole treated groups. The Serum Glutamyl Pyruvate Transaminase (SGPT) level was also increased in all treated groups except mebatic treated group as compared to control treated group. When all treated groups were compared to each other on 12th and 24th day, the level of SGPT was increased insignificantly in all treated group except mebatic treated group as well as control treated group (Fig. 7, 8).

Effect of Mebatic on Malondialdehyde Level

The malondialdehyde level was significantly increased in all treated groups as compared to control normal saline treated group. In case of mebatic treated group, the level was reduced and come near to control level after 12 days of treatment. When malondialdehyde level was compared in ofloxacin, ornidazole as well as metronidazole alone treated groups on 12th and 24th day treatment, the level was insignificantly increased about 15.6, 13.27 and 5.65%, respectively in all treated groups. In case of mebatic treated group, the level was minorly decreased about 0.36% (Fig. 9).

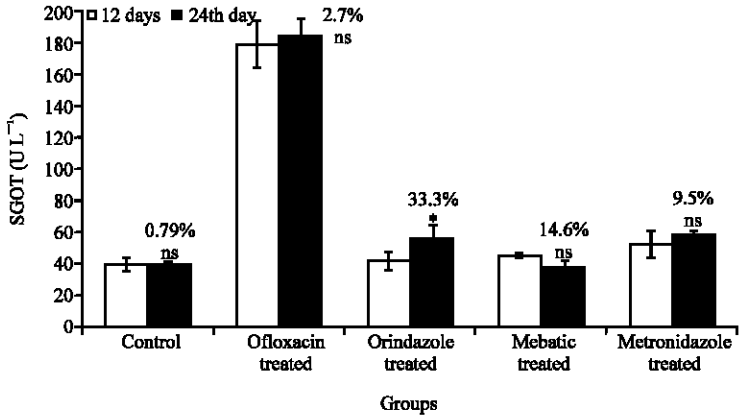

Fig. 7: Values are represented in Mean±SD. All the data were compared control vs. all treated groups and vs. each other. The statistical data were measured by Newman keul test. The percentage change was observed between 12th and 24th day. Toxicity study of Mebatic drug vs. Ofloxacin, Ornidazole and Metronidazole in SGOT level on 12th and 24th day. *p<0.05, ns: Not significant

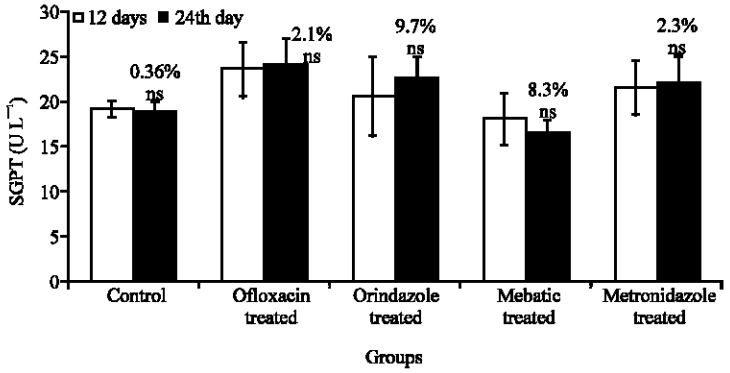

Fig. 8: Values are represented in Mean±SD. All data were compared control vs. all treated groups and vs. each other. The statistical data were measured by Newman keul test. The percentage change was observed between 12th and 24th day. Toxicity study of Mebatic drug vs. Ofloxacin, Ornidazole and Metronidazole in SGPT level on 12th and 24th day. ns: Not significant

Ofloxacin, ornidazole and metronidazole drugs alone causes 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, necrotizing vasculitis, allergic tubular nephritis or a tubular necrosis (Lomaestro, 2000; Montagnac *et al*., 2005). Apart from this, fluroquinolones and nitroimidazoles are also highly involved in serious hepatotoxic consequences (Clark *et al*., 2001). 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). Present results showed that a single therapy of ofloxacin, ornidazole and metronidazole drugs increases hepatotoxicity and renal toxicity. It was observed that SGPT and SGOT level was

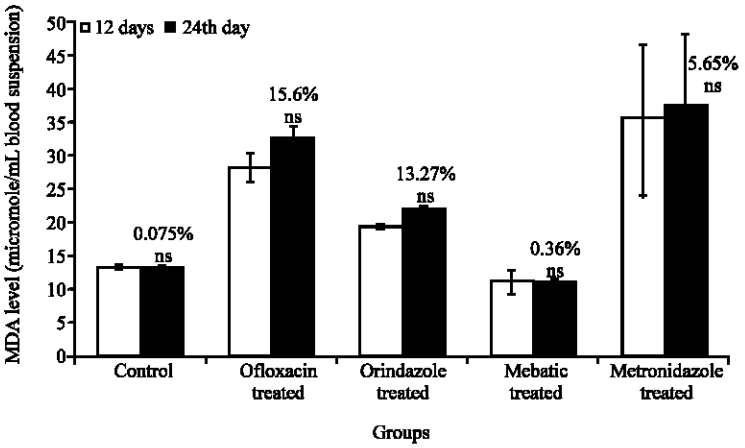

Fig. 9: Values are represented in Mean±SD. All the data were compared control vs. all treated groups and vs. each other. The statistical data were measured by Newman keul test. The percentage change was observed between 12th and 24th day. Toxicity study of Mebatic drug vs. Ofloxacin, Ornidazole and Metronidazole in MDA level on 12th and 24th day. ns: Not significant

increased in ofloxacin, ornidazole as well as metronidazole alone treated groups as compared to control normal saline treated group. When these treated groups were compared with each other on 12th and 24th day treatment, the levels were increased. Similarly, there was increase in the parameters related to kidney function such as creatinine, urea, ALP, bilirubin and uric acid levels in ofloxacin, ornidazole as well as metronidazole alone treated groups as compared to control group. The hepatic and renal parameters were reduced in a fixed dose combination therapy of ofloxacin plus ornidazole treated group and come almost near to control level. Present results stated that fixed dose combination of ofloxacin plus ornidazole i.e., mebatic is beneficial than individual therapy of ofloxacin, ornidazole and metronidazole. Nitroimidazole is considered clearly hepatotoxic, renal toxic with reports of diffused damage of parenchymal and nonparenchymal liver cells as initial stage of hepatic damage using electron microscopy and biochemical markers in serum with emphasis of pathophysiology. In the present study, the level of malondialdehyde was also significantly increased in ofloxacin, ornidazole and metronidazole alone treated groups as compared with control group. When malondialdehyde level was compared on 12th and 24th day to each groups, the level was increased in ofloxacin, ornidazole and metronidazole alone treated groups except mebatic treated group. The level of malondialdehyde was increased in ofloxacin, ornidazole and metronidazole alone treated groups due to excessive generation of reactive oxygen species. It means that fluroquinolones and nitroimidazole causes free radical generation.

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 exerts its devastating effects by directly damaging cellular proteins, lipids and DNA, or indirectly, by affecting normal cellular signaling and gene regulation and antioxidants. Antioxidants have been reported to provide protection in various pathological conditions (Kumar *et al.*, 2007a; Tikoo *et al.*, 2008). 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 Gram-positive strains are moderately susceptible (Miller and Shah, 1997; Messadi *et al*., 2008). Mebatic is a fixed dose combination of ofloxacin and ornidazole along with VRP006 (trade secrete). The role of VRP006 is potent antimicrobial, cytotoxicity and antioxidant properties which inhibits growth and free radical mediated damages and improves hepatotoxicity and renal toxicity. 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). The additive advantage over monotherapy is that both drugs act on DNA and provide sequential block on bacterial DNA to contribute to synergistic activity. In the present study, renal and hepatic enzymes were reduced in fixed dose combination therapy than alone therapy. Hence, fixed dose combination therapy of ofloxacin plus ornidazole that is mebatic drug is safe and it does not causes any alteration in liver and kidney.

CONCLUSION

On the basis of present findings, it was concluded that mebatic (ofloxacin plus ornidazole) drug is safe than alone therapy and it improved the hepatic and renal enzyme along with reduced free radical mediated damage.

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