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RESEARCH ARTICLE

A STUDY ON THE PHARMACOKINETIC ALTERATIONS OF MOXIFLOXACIN WITH PYRAZINAMIDE AND ETHAMBUTOL IN HEALTHY VOLUNTEERS

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ABSTRACT

The study was aimed to know the pharmacokinetic interactions between moxifloxacin and pyrazinamide and also the pharmokinetic interactions between moxifloxacin and ethambutol and to know about the clinical significance. The study population was 12 healthy male volunteers, the duration of study was 13 days for each healthy volunteer and period of study was one year and it was a randomized open labelled non comparative prospective study. The pharmacokinetic variables were calculated based on plasma concentration of moxifloxacin alone and in combination with pyrazinamide and also in combination with ethambutol at different points from 0 -12 hours. The steady state mean pharmacokinetic variables such as peak concentration (C_{max}), time at which C_{max} is attained (T_{max}), area under curve (AUC), clearance (Cl) and half-life ($t^{1/2}$) were calculated and statistical analysis was done using student 't' test and considered significant ($P = < 0.05$). The study concluded that there are no pharmocokinetic interactions between moxifloxacin and pyrazinamide and between moxifloxacin and ethambutol. Hence Moxifloxacin can be administered along with pyrazinamide and ethambutol for better patient compliance, increased cure rates and to reduce the duration of the anti-tuberculosis treatment.

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INTRODUCTION

Every year approximately1.8 million persons develop tuberculosis (TB) of which 0.8 million cases are smear positive and about 4.17 lakh people die of TB. The optimal treatment of tuberculosis is challenging because of the increase in both drug susceptible and multi drug resistance strains (Park, K. 2005).With the recommended six months regimen, by the end of the third month, virtually all the patients should be culture negative. When a patient's sputum culture remains positive at or beyond three months, treatment failure and drug resistance should be suspected (Eugene Braunwald *et al*., 2001). Because of microbial resistance it may be necessary to resort to 'second line drugs' and category of agents includes moxifloxacin, gatifloxacin, ethionamide, paraaminosalicylic acid, cycloserine, amikacin, kanamycin, capreomycin and linezolid (Lawrence L *et al*., 2006). The current TB regimen requires six months duration of therapy to treat tuberculosis effectively. Though the treatment of tuberculosis with multidrug therapy witness a dramatic improvement in control of disease, the main problem encountered in implementation of these regimen are prolonged course of therapy and poor compliance. The poor compliance may be due to pharmacokinetic interaction which may lead to toxicity.

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Hence we decided to conduct a study to look into pharmacokinetic interactions of moxifloxacin with pyrazinamide and with ethambutol respectively to find out the possibility of reduction of duration of antituberculous treatment from six months when the moxifloxacin is added to pyrazinamide or ethambutol.

MATERIALS AND METHODS

Study Design: A randomized open labelled non comparative prospective study

Study centre: Clinical pharmacology unit

- Madras Medical college and Govt General Hospital, Chennai
- Tuberculosis Research centre (ICMR)

Study population: Healthy male volunteers

Sample size: 12

Duration of study: 13 days for each volunteer

Study period: one year

Inclusion criteria

- Healthy male
- Age 20- 50years
- BMI 18.5 to 25
- Normal hematological and biochemical parameters
- HIV seronegative
- Those who are willing to give written informed consent

Exclusion criteria

- Smokers
- Alcoholics
- Hypertensive, diabetic, and those suffer from hepatic and renal disorder
- Any major systemic illness
- Those who have taken medications for any illness at the time of screening.

Screening visit

Hematology: Blood total count, differential count, ESR and HB%

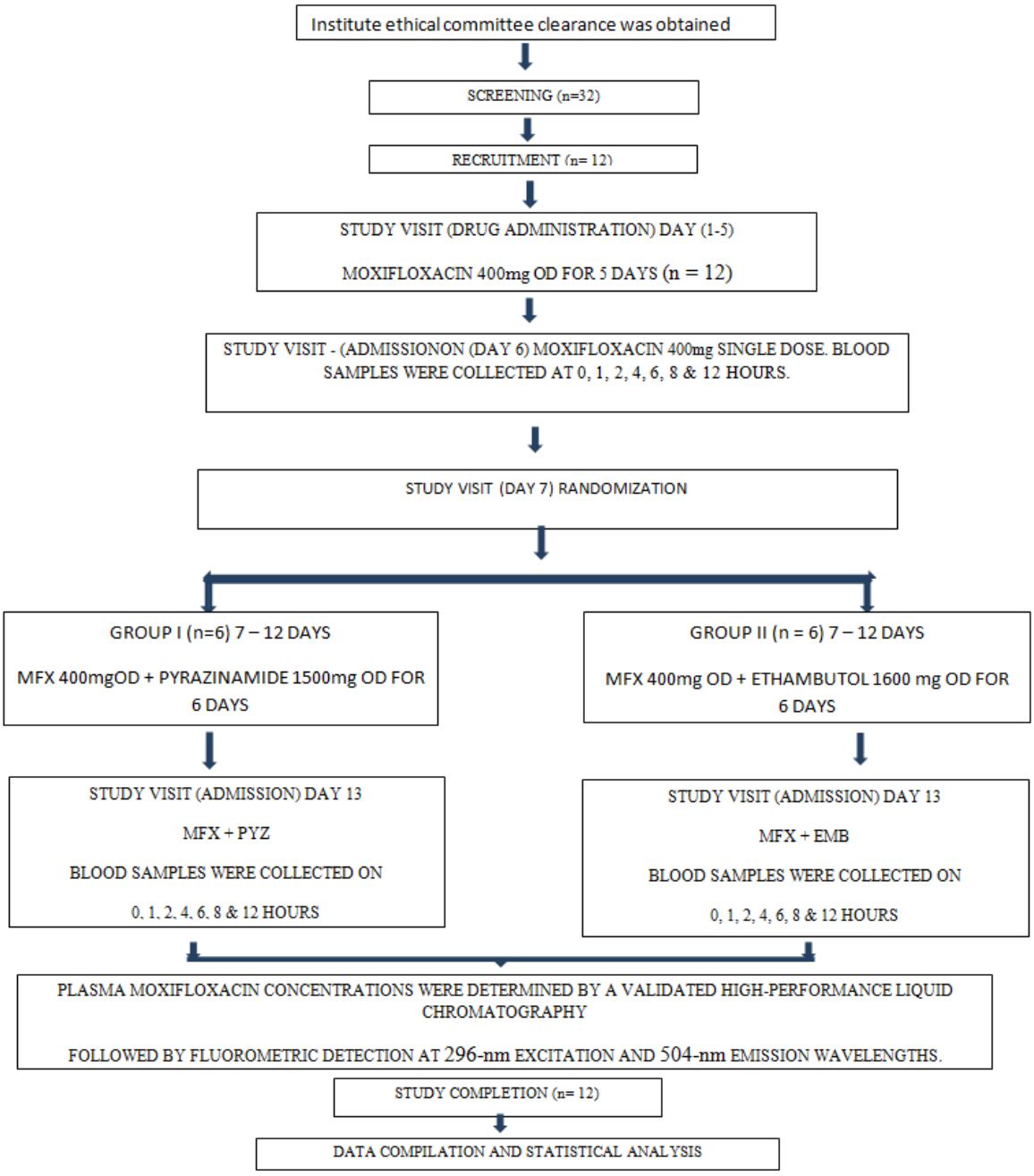
Biochemistry: Blood sugar, urea, creatinine, SGOT, SGPT,

HIV screening, ECG and X-ray chest.

The Moxifloxacin concentration in plasma was determined by High - Performance Liquid Chromatography (HPLC) and

Methods

Study Procedure Flow Chat



Fluorescent detection. Mobile phase consists of acetonitrile and Tetra butyl ammonium hydrogen sulphate. Ofloxacin was used as internal standard. Fluorescent detection was performed at an excitation wavelength of 296nm and an emission wavelength of 504nm. The intra assay accuracy range from 4% to 7.3% and intra assay precision range from 3.3% to 6.8%.

RESULTS

The demographic details of six healthy volunteers who received moxifloxacin with pyrazinamide depicts in Table 1. In Table 2 shows the demographic details of six healthy volunteers received moxifloxacin with ethambutol.

Table 1. Demographic details of six healthy volunteers who received Moxifloxacin with Pyrazinamide

S.NO	Details	Mean (range)
1.	Age (Years)	25.5
2.	Weight (Kg)	59.5
3.	Height (CM)	162.5
4.	BMI wt/m^2	22.8

Table 2. Demographic details of six healthy volunteers who received Moxifloxacin with ethambutol

S.NO	Details	Mean (range)
1.	Age (Years)	30.3
2.	Weight (Kg)	58.3
3.	Height (CM)	164.7
4.	BMI (wt/m^2)	22

The pharmokinetics variables were calculated based on plasma concentration of moxifloxacin alone and in combination with pyrazinamide in six volunteers as well in another group of six volunteers taken moxifloxacin alone and in combination with ethambutol.

The steady state mean pharmacokinetic variables such as peak concentration (C_{max}), time at which C_{max} is attained (T_{max}), area under the concentration - time curve (AUC), clearance (Cl) and half-life ($t^{1/2}$) were calculated. The plasma concentration of moxifloxacin and moxifloxacin with pyrazinamide were plotted at different time points (Fig 1) and the plasma concentration of moxifloxacin and moxifloxacin with ethambutol were shown in Fig 2. Statistical analysis of data was performed. The data were expressed as mean +/- standard deviation. The significance of difference in the pharmacokinetic parameters of moxifloxacin when administered alone or moxifloxacin with pyrazinamide and moxifloxacin with ethambutol were calculated using student 't' test and ($P < 0.05$) was considered statistically significant. Hence there are no pharmacokinetic interactions between moxifloxacin with pyrazinamide and moxifloxacin with ethambutol.

DISCUSSION

Tuberculosis is a specific infectious disease caused by Mycobacterium tuberculosis. In 1882 Robert Koch discovered the tubercle bacilli, although *M. tuberculosis* is the most important of the mycobacterial pathogens, many other mycobacteria have been discovered which produces tuberculosis like lesion in both animals and man (G.S. Sainani, 1999). Surveillance in several areas in India has found that 3.4% of new patient have multi drug resistant tuberculosis (Govt of India, 2004). Moxifloxacin is the most active fluoroquinolone against the strains that are resistant to first line drugs. Moxifloxacin should be used in combination with two or more often active agents (Katzung, 2007). The newer synthetic fluoroquinolonesmoxifloxacin is effective against Mycobacterium tuberculosis and it does not have cross resistance to other classes of TB drugs (Katzung *et al*., 1997).

Table 3. Pharmokinetics of Moxifloxacin and interaction with pyrazinamide

Healthy subject	C_{max}	T_{max}	AUC (0-12)	Cl	$t^{1/2}$
MFX (n=6)	4.3767 ± 0.7913	1.83 ± 0.4082	35.4599 ± 5.99886	6.9590 ± 1.3870	8.69 ± 1.16
MFX + PYZ	4.54 ± 0.91	2 ± 1.10	35.51158 ± 7.875818	7.59088 ± 3.00387	8.15622 ± 2.26847
MFX/ MFX + PYZ	t = 0.33 P = 0.75	t = 0.35 P = 0.73	t = 0.01 P = 0.91	t = 0.64 P = 0.46	t = 0.52 P = 0.61

Cmax – Peak plasma concentration, **Tmax-** Time to attain Cmax, **AUC (0-12)**- Exposure, **Cl-** Plasma clearance, **$t^{1/2}$-** Half-life.

Table 4. Pharmokinetics of Moxifloxacin and interaction with Ethambutol

Healthy subject	C_{max}	T_{max}	AUC (0-12)	Cl	$t^{1/2}$
MFX (n=6)	4.6217 ± 0.8449	2.000 ± 1.0954	35.0145 ± 2.8200	7.2655 ± 1.5259	7.98 ± 3.15
MFX + EMB	4.40 ± 0.26	2.50 ± 1.22	35.5261 ± 2.403	6.3710 ± 0.4663	9.0520 ± 1.0165
MFX/ MFX + EMB	t = 0.61 P = 0.55	t = 0.54 P = 0.60	t = 0.33 P = 0.74	t = 0.137 P = 0.19	t = 0.58 P = 0.56

Cmax – Peak plasma concentration, **Tmax**– Time to attain Cmax, **AUC (0-12)** - Exposure, **Cl-** Plasma clearance, **$t^{1/2}$**– Half-life.

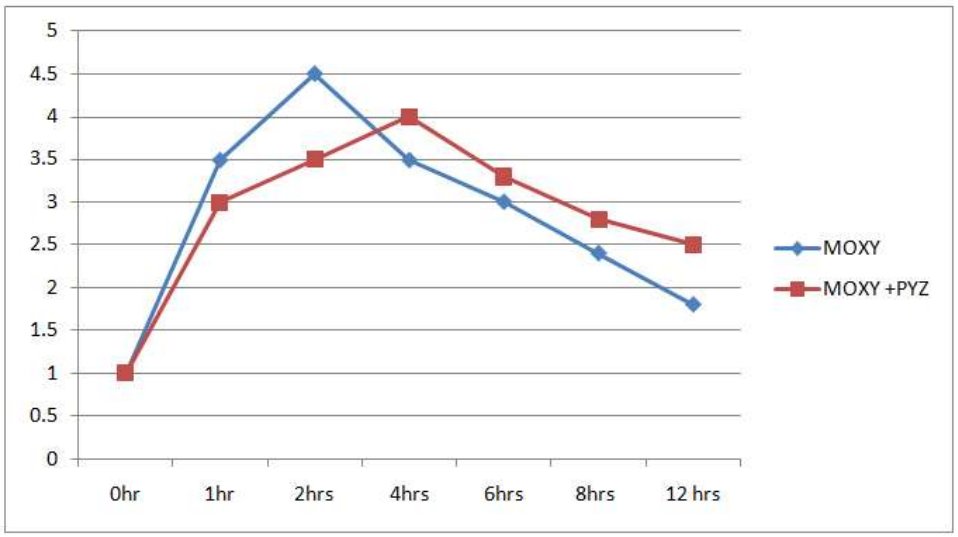


Fig. 1. Mean Moxifloxacin steady state plasma concentration versus time for moxifloxacin alone and moxifloxacin with pyrazinamide

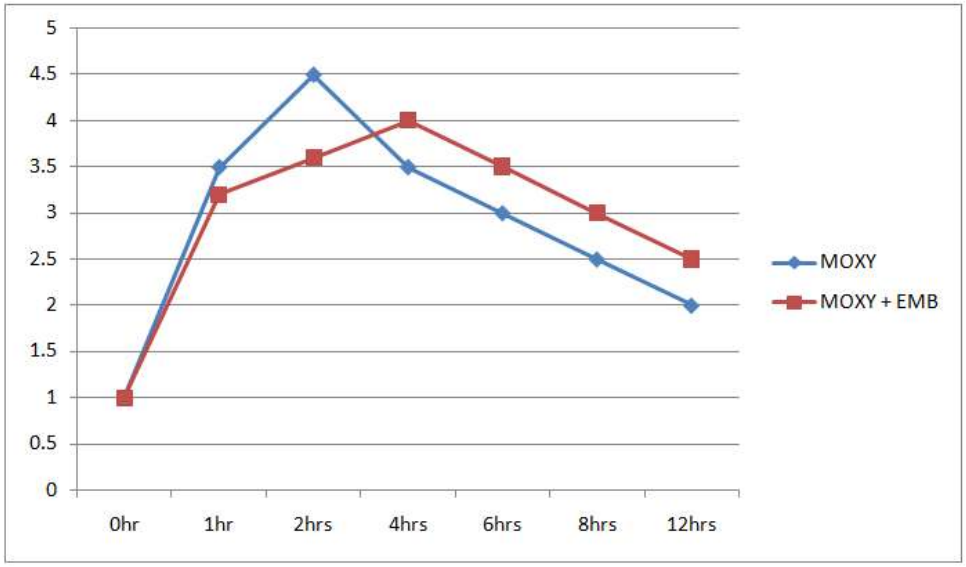


Fig. 2. Mean Moxifloxacin steady state plasma concentration versus time for moxifloxacin alone and moxifloxacin with Ethambutol

Moxifloxacin has good bactericidal activity against Mycobacterium tuberculosis with MIC_{90}0.25mg/L (Gilespie *et al*,. 1996).The bioavailability of moxifloxacin is 91.8% (Ballow *et al.,* 1999). The median distribution volume is 94.90L and it is metabolized to an N-sulfate conjugate and an acyl glucuronide in humans. The urinary excretion of the unchanged drug account for 19- 22% (Moise, 2000). The mode of action it inhibits bacterial topoisomerase 2 (DNA gyrase) and topoisomerase 4moxifloxacin have drug interactions with antacid containing aluminium or magnesium ions, iron, zinc and minerals which inhibits its absorption (Pestova *et al.,* 2000, Colleen *et al.,* 2001). Moxifloxacin was evaluated alone and in combination with rifampin, isoniazid, pyrazinamide, ethambutol and ethionamide in a murine model (Ginsburg *et al.,* 2005, Chaisson 2007). Moxifloxacin drug combination speeds up treatment of tuberculosis. Comments by study of senior author Richard E Chaission MD, a professor of Medicine, epidemiology and international health at the Johns Hopkins University School of medicine and founding director of its centre for tuberculosis research reported that "This is the most compelling evidence in nearly 25 years that moxifloxacin drug combination works better than the current gold standard at curing TB infection (Richard Chaission, 2007). A team of tuberculosis experts at John Hopkins University in Brazil have evidence that substituting the antimicrobial moxifloxacin in the regimen of drugs used to treat the highly contagious form of lung disease could dramatically shorten the time needed to cure the illness from six months (Nuermberger *et al.,* 2004).

The study conducted by Sullivan *et al.* and Stass *et al.* which dealt with the pharmokinetics, safety and tolerability of ascending single doses of moxifloxacin, a new 8 methoxy

quinolone administered to healthy subjects were assessed in a randomised, double blind placebo controlled study in which healthy male volunteers received either 400mg of moxifloxacin once daily or a placebo once daily for 10 days. Plasma concentration of moxifloxacin on day 1 and 10 were measured by high pressure liquid chromatography and fluorometric detection. The pharmacokinetic parameters $C_{max,}$ AUC were estimated on day 1, the mean C_{max} was 3.4µg/ml and mean AUC_{0-24} (0-24 hours) was 30.2µg/ml/hr. On day 10 the C_{max} was 4.5µg/ml and mean AUC_{0-24} (0-24 hours) was 4.8µg/ml/hr. This study shows moxifloxacin increases theC_{max} and AUC (Sullivan *et al.,* 1999*;* Stass *et al.,* 1998). In our study moxifloxacin 400mg was given orally for twelve healthy volunteers for six days. The pharmacokinetics parameters C_{max}, AUC were obtained, the mean C_{max} was 4.3µg/ml and mean AUC 0-12 hours was 35.5/µg/ml/hr which is almost similar to the studies conducted by Sullivan *et al.* (Table 3, 4) The study of the pharmacokinetic drug interactions due to administration of moxifloxacin with pyrazinamide and moxifloxacin with ethambutol has not been done earlier based on the data available. Hence it was decided to study the pharmacokinetic interactions of moxifloxacin with pyrazinamide andethambutol and the data obtained were analysed in detail. The P value of C_{max}, T_{max}, AUC (0-12hours), Cl, and $t^{1/2}$in the pharmacokinetics of moxifloxacin with pyrazinamide are 0.75, 0.73, 0.91, 0.46 and 0.61respectively (Table 3).

The highest P value is in AUC (0 – 12hours) is 0.91 which is insignificant (Table 3). This infers that pyrazinamide does not affect the moxifloxacin kinetics. Likewise the P value of C_{max}, T_{max}, AUC (0- 12hours) Cl and $t^{1/2}$in the pharmacokinetics of moxifloxacin with ethambutol are 0.55, 0.6, 0.74, 0.19 and 0.56 respectively (Table 4). The highest P value is in AUC (0 – 12 hours) 0.74 which is insignificant. This infers the ethambutol does not affect the moxifloxacin kinetics. The mean steady state plasma concentration versus for moxifloxacin alone and moxifloxacin with pyrazinamide as shown in (Fig. 1) and the mean moxifloxacin steady state plasma concentration versus time for moxifloxacin alone and moxifloxacin with ethambutol as shown in (Fig. 2) showed no significant variation between the two groups.

Conclusion

From the study it can be concluded that

- There is no pharmacokinetic interaction between Moxifloxacin and Pyrazinamide.
- There is no pharmacokinetic interactions between Moxifloxacin and Ethambutol
- Hence Moxifloxacin can be administered along with pyrazinamide and ethambutol for better patient compliance, increased cure rates and to reduce the duration of the anti-tuberculosis treatment.

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REFERENCES

Ballow, C., Lettieri. J., Agarwal, V., Liu, P., Stass, H and Sullivan, JT. 1999. Absolute bioavailability of Moxifloxacin. *Clin Ther*., 21(3):513-522.

Chaisson, R.E. 2007. A randomised, placebo controlled trial of Moxifloxacin versus ethambutol in the initial phase of tuberculosis therapy in Brazil. 47th Interscience conference on antimicrobial agents and chemotherapy, Chicago, Abstract L – 736- A.

Colleen, M.C., Melinda, K.L., Neil, K and Brian Edwards. 2001. Moxifloxacin: Clinical efficacy and safety. *AMJ health system Pharm*., 58:379& 388.

Ed–Sainani, G.S. 1999. API Text book of Medicine, Association of Physicians of India; Mumbai, 6th edition.Pp.55.

Eugene Braunwald., Anthony, S., Fauci Dennis L., Longo, J., and Zarry Jameson. Harrisons principles of Internal Medicine, 15th edition, Volume I; Mcgraw Hill: New York, USA,pp.1020 & 1032.

Gilespie, S.H and Billington, O. 1999. Activity of moxifloxacin against mycobacteria. *Journal of Antimicrobial Chemotherapy*., 44: 393 – 395.

Ginsburg, A.S., Sun, R and Calamita, H. 2005. Emergence of fluroquinolone resistance in Mycobacterium tuberculosis during continuously dosed moxifloxacinmonotherpy in a mouse model. Antimicrob Agents Chemother. 49(9): 3977–3979.

Govt of India, 2004. Annual report, 2003 -2004, Minister of Health and Family welfare, New Delhi.

Katzung, B.G. 2007. Ed; Basic and clinical pharmacology. 10th edition. McGraw Hill: New york, USA, pp. 777.

Lawrence, L., Brunton., John S Lazo., and Keith L Parker. 2006. (eds) Goodman and Gilmans. The pharmacological basis of therapeutics, 11thedition. McGraw Hill: New York, USA., pp. 1203 & 1211.

Moise, PA. 2000. Pharmacokinetics and metabolism of Moxifloxacin. Drugs today., 36(4):229.

Moxifloxacin drug combo speeds up treatment of tuberculosis Medical studies trial published 19 September – 2007 WHP. www.hopkinsmedicine.org.

Nuermberger, E.L., Yoshimatsu, T., Tyergis Obrien, R.J., Bemon, A.N and Chassian R.E. 2004. Moxifloxacin containing regime greatly reduces time to culture conversion in murine tuberculosis. *Am. J. Respir. Crit. Care Med*., 169:421-426.

Park, K. 2005. Park's Textbook of preventive and social medicine.18thedition. Banarsidas Bhanot Publishers: pp.147 & 335 -336.

Pestova, E., Millichap, J.J andNoskin, G.A. 2000. Intracellular targets of Moxifloxacin; A comparison with other fluroquinolones. *J Antimicrob Chemother*., 45: 583-590.

Stass, H., Dalkhoff, A., Kubitza, D and Schuhly U. 1998. Pharmacokinetics safety and tolerability of ascending single doses of Moxifloxacin a new 8 methoxy quinolone, administered to healthy subjects. *Antimicrob Agents Chemother*., 42; 2060-2065.

Sullivan, J.T., John, L., Vipin, A., George, J.K., Philip, T.L., Susan, W and Allen, H.H.1999. Pharmacokinetics of a Once – Daily oral dose of Moxifloxacin (Bay 12 - 8039), a new Enantiomerically pure 8 – methoxy Quinolones. Antimicrob Agents Chemother., 43(11): 2793–2797.

Woodcock, J.M., Andrews, J.M., Boswell, F.J., Brenwald, N.P and Wise, R. 1997. In vitro activity of Bay 12-8039 a new fluoroquinolone. Antimicrob Agents Chemother., 41:101 – 106.

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