

Penetration of Moxifloxacin into Aqueous Humour and Plasma following Oral Administration among Cataract Surgery Patients

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Abstract :

Introduction : Endophthalmitis is one of the most serious complication following cataract surgery. Topically administered antibiotics are usually given at frequent interval starting few days before surgery to achieve desired concentration in aqueous humour for the prevention of endophthalmitis. Moxifloxacin significantly penetrates into aqueous humour after oral administration that may improve patient compliance.

Objectives : Present study was designed to evaluate the aqueous and plasma concentrations of moxifloxacin administered orally at different time interval before cataract surgery.

Methodology : Prospective study of 25 patients scheduled for cataract surgery. Patients were divided into 5 Groups (Group A, B, C, D & E) and each Group comprises of 5 patients. Single dose of oral moxifloxacin – 400 mg tablet was given to each Group at different time schedule i.e. 2, 4, 8, 12, and 18 hours before aqueous humour sampling accordingly to Group A, B, C, D & E respectively. Topical moxifloxacin eye drop (0.5%) - 1 drop 6 times daily for 3 days before surgery and 1 drop 4 times on the day of surgery was also given to the all subgroups for the ethical reasons. The antibiotic concentration in aqueous aspirates and plasma were determined by using HPLC.

Results : Aqueous and plasma concentrations of moxifloxacin was maximum in Group A and least in Group E.

Conclusion : Administration of single dose of oral moxifloxacin increases the aqueous concentration of moxifloxacin for the prevention of post operative endophthalmitis in cataract surgery patients.

Keywords : Aqueous humour, cataract surgery patients, oral moxifloxacin.

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I. Introduction

Bacterial endophthalmitis is one of the most serious complication following intraocular operation like cataract surgery. Commonest micro-organisms involved in endophthalmitis are either gram-positive (e.g. *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Streptococci*, *Propionibacterium acnes*) or gram-negative (*Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Serratia marcescens*) bacteria.¹ Systemically administered antibiotics have to penetrate the existing blood-ocular barriers to reach levels in the anterior chamber much higher than the minimal inhibitory concentrations (MICs) in order to eliminate the micro-organisms potentially. Second and third generation systemic fluoroquinolones have been found to have significant penetration into aqueous humour and less so into the vitreous body, with concentrations usually exceeding MICs of pathogens implicated in intraocular infections.^{2,3} Due to disadvantages of systemic routes, the topical ophthalmic preparations of fluoroquinolones were developed to achieve required concentration of drugs in aqueous humour for prevention of endophthalmitis. But topically administered drugs are used frequently several times starting few days before surgery to achieve desired aqueous humour concentration of the antibiotic for the prevention of endophthalmitis. So, patient compliance is a very important factor regarding the administration of drugs. Moxifloxacin is a new fourth generation fluoroquinolone with a broad spectrum of activity.⁴ It has been found to be the most potent fluoroquinolone for gram-positive bacteria including methicillin resistant *Staphylococcus aureus* (MRSA) and ciprofloxacin resistant *Staphylococcus aureus* and equally potent as other fluoroquinolones against gram-negative bacteria.¹ Central nervous system (CNS) stimulating effect of some fluoroquinolones may be enhanced with co-administration of non-steroidal anti-inflammatory drugs (NSAIDs), resulting in neuroexcitation and/or seizures; but this effect has not been observed with moxifloxacin.⁴ With this knowledge a clinical study was designed to measure and evaluate the concentration of moxifloxacin, used orally as a single dose (400mg) at different time interval, in the aqueous humour as well as in the blood simultaneously, collected just before cataract surgery. Topical moxifloxacin was also used for the ethical reason.

II. Materials And Methods

For this prospective, parallel, randomized, unicentric study; patients scheduled for routine cataract surgery in the Dept. of Ophthalmology, R.G.Kar Medical College & Hospital, Kolkata were included. The protocol was approved by the Institutional Ethics Committee (IEC). Screening with inclusion and exclusion criteria 25 patients were selected and written consents were obtained from them. Individual Case Report Form (CRF) was properly filled up from out-patient (OPD) ticket and by interrogation of the patients. Included patients were above 40 years of age, undergoing cataract surgery and otherwise healthy. Patients with evidence of intraocular inflammation, hepatic or renal failure, or history of allergic reactions to fluoroquinolones, oral or topical antibiotic treatment for at least the preceding 2 weeks and previous operation in that eye were excluded. Patients were divided into five Groups (Group A, B, C, D & E) and each Group comprises of five patients. Single dose of oral moxifloxacin – 400 mg tablet was given to each Group at different timeschedule i.e. 2, 4, 8, 12, and 18 hours before aqueous humour sampling accordingly to Group A, B, C, D & E. Topical moxifloxacin eye drop (0.5%) - 1 drop 6 times daily for 3 days before surgery and 1 drop 4 times on the day of surgery was also given to the all subgroups, as this is followed routinely at R. G. Kar Medical College & Hospital, Kolkata for the cataract surgery patients to prevent bacterial endophthalmitis. Participants were scheduled to have extracapsular cataract extraction (ECCE). While the patient was being prepared for operation after peribulbar anesthesia 5 ml blood was obtained. At the initial stage of operation, 0.1 ml of aqueous humour was aspirated from the anterior chamber through a partial thickness limbal incision. Both the samples were then prepared for estimation of moxifloxacin levels by using High Performance Liquid Chromatography (HPLC) according to method of Isavadharm T et al.⁵ with some modifications. Centrifuging blood samples immediately afterwards, plasma was extracted. Then 0.5 ml plasma was mixed with 1.5 ml of HPLC grade methanol and 0.1 ml aqueous humour was mixed with 0.5 ml of HPLC grade methanol. Both samples were kept in 2 to 8^oC and transferred immediately maintaining the temperature for assessment of antibiotic level. The mobile phase consisted of 0.1 M phosphoric acid adjusted to pH 2.5 with a solution of 45% potassium hydroxide and acetonitrile mixed in a ratio of 70:30% (v/v). The flow rate of mobile phase was 1.2 mL/ min and the eluent was monitored with Diode Array Detector adjusted wavelength at 290 nm. This mixture was subjected to membrane filtration. Standard and sample (20 µl) were injected by Hamilton Syringe into the injector port of liquid chromatograph. The residues were estimated after comparing with external standard.

Calibration : A stock solution of 100 ppm of analytical grade moxifloxacin was prepared in methanol as standard. The moxifloxacin concentration in plasma and aqueous humour was calculated using following equation.

Concentration of moxifloxacin in plasma and aqueous humour (µg/ml) =

a_1 = Area of standard chromatogram

a_2 = Area of sample chromatogram

V_1 = Initial volume of sample before processing (ml)

V_2 = Final volume of sample after processing (ml)

C = Standard strength of moxifloxacin 100 ppm.

$$\frac{a_2 \times V_2 \times C}{a_1 \times V_1}$$

Statistical analysis was done by one way Analysis of Variance (ANOVA) with post hoc test Dunnet multiple comparison test and Tukey- Kramer multiple comparison test were used to assess the statistical significance of differences in means. P value < 0.05 was considered as significant.

III. Results

After scrutinizing the CRF form the age of the patients were found between 50 to 70 years. According to the demographic profile (Table 1) and vital parameters (Table 2) of the recruited subjects all the groups are comparable. Detail results after laboratory estimation are summarized in Table 3. Mean moxifloxacin level in aqueous humour ranged between $1.82 \pm 0.32 \mu\text{g/ml}$ (at 18 hour group) to $4.35 \pm 0.24 \mu\text{g/ml}$ (at 2 hour group) and maximum in 2 hours group (i.e. Group A) and least in Group E (i.e. 18 hours before sampling). Mean moxifloxacin level in plasma ranged between $2.61 \pm 0.24 \mu\text{g/ml}$ (at 18 hour group) to $7.58 \pm 0.87 \mu\text{g/ml}$ (at 2 hour group) and maximum in 2 hours group (i.e. Group A) and least in Group 3 (i.e. 18 hours before sampling).

IV. Discussion

The goal of our study was to evaluate the aqueous concentration difference of moxifloxacin applied orally as a single dose at different intervals. The plasma concentration difference was also compared. Antibiotic penetration and aqueous concentration in aqueous humour in respect of different members of fluoroquinolones have been compared in several studies.⁶ An advantage of moxifloxacin is its oral administration and good aqueous and vitreous humour penetration.⁷⁻¹⁰ It displays linear pharmacokinetics in blood after a 400 mg dose (when administered orally or intravenously) with half life of moxifloxacin is 11.5-15.6 hours.¹¹ As moxifloxacin was found to be the most potent fluoroquinolone¹ and has been found high corneal permeability¹², it was selected for our study. But, to attain the desired plasma concentration in aqueous humour for the prevention of

post-operative endophthalmitis, topical moxifloxacin must have to be administered at frequent intervals and to be started few days before surgery as the standard protocol. So, patient compliance is a very important factor. Adequate information was not available regarding the aqueous and plasma concentration of moxifloxacin after oral administration. That's why we designed this study. Topical moxifloxacin was also given to all the patients for the ethical reasons. Prophylactic moxifloxacin treatment before cataract surgery provides optimal antibiotic concentration in aqueous humour, which reduces bacterial population on eyelids, cornea and conjunctiva. The optimal concentration is able to prevent development of post-operative endophthalmitis following cataract surgery.^{12,13} Administration of topical agents on the day of surgery does not allow adequate exposure time, rather the agents are being applied the days before surgery is more effective.¹³ Based on these knowledge, topical moxifloxacin was started 3 days before surgery and few hours preoperatively on the day of surgery in different dose schedule in our study along with single dose of oral moxifloxacin 400 mg tablet was given at different time interval to the different groups.

The result of mean aqueous humour concentration of moxifloxacin in our study was minimum as $1.82 \pm 0.32 \mu\text{g/ml}$ (at 18 hour Group, i.e. Gr E) and maximum as $4.35 \pm 0.24 \mu\text{g/ml}$ (at 2 hour Group, i.e. Gr A). Mean moxifloxacin level in plasma was also least ($2.61 \pm 0.24 \mu\text{g/ml}$) in Group E and maximum ($7.58 \pm 0.87 \mu\text{g/ml}$) in Group A.

Though it is not comparable due to the limited sample size, still the concentration achieved in our study even in Group E was matched with the results (mean average aqueous humour concentration of moxifloxacin was $1.72 \pm 0.82 \mu\text{g/ml}$ when used alone topically) of other studies^{14,15} The aqueous concentration of moxifloxacin was quite higher among rest of the Groups (i.e. Group A to D).

In conclusion, according to the results by adding a single dose of oral moxifloxacin (400 mg tablet) shows a significant higher concentration of antibiotic level in aqueous humour that may be better patient compliance without documentation of any serious adverse effects of the drug. It was just a pilot study, further study with larger sample size is needed to confirm the results.

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Table 1 : Demographic profile of recruited subjects :

Parameter	A (Topical + Oral moxifloxacin 2 hour before surgery)	B (Topical + Oral moxifloxacin 4 hour before surgery)	C (Topical + Oral moxifloxacin 8 hour before surgery)	D (Topical + Oral moxifloxacin – 12 hour before surgery)	E (Topical + Oral moxifloxacin – 18 hour before surgery)	p value
Mean age (years) ± SD (range)	55.2 ± 8.81	60.8 ± 8.71	56.8 ± 9.76	57.8 ± 6.72	58.6 ± 5.69	ns
Sex (M– Male, F – Female) No. (%)	M – 3 (60), F –2 (40)	M - 2(40), F –3 (60)	M – 2 (40), F – 3 (60)	M - 3(60), F –2 (40)	M – 3 (60), F –2 (40)	ns
Body weight (Kg) Mean ± SD (range)	53.5 ± 6.19	54.7 ± 5.33	56.1 ± 5.38	57.2 ± 6.42	52.5 ± 5.92	ns

- Abbreviations: SD = Standard deviation, ns = not significant
- p-values from Student’s unpaired t test for all variables except comparing of sex, for which Fisher’s Exact Probability Test was applied.

Table 2 : Vital parameters of recruited subjects :

Parameter	3A (Topical + Oral moxifloxacin 2 hour before surgery)	3B (Topical + Oral moxifloxacin 4 hour before surgery)	3C (Topical + Oral moxifloxacin 8 hour before surgery)	3D (Topical + Oral moxifloxacin –12 hour before surgery)	3E (Topical + Oral moxifloxacin – 18 hour before surgery)	p value	
PPBS (mg%) Mean ± SD (range)	114.3 ± 6.71	124.2 ± 5.92	134.3 ± 4.65	128.3 ± 5.22	121.3 ± 4.91	ns	
Pulse / minute Mean ± SD (range)	77.2 ± 5.23	72.2 ± 4.20	80.2 ± 5.27	74.2 ± 4.48	78.2 ± 5.26	ns	
BP (mmHg)	SBP Mean ± SD (range)	126.8 ± 5.72	136.2 ± 4.32	126.4 ± 6.98	128.4 ± 7.16	127.2 ± 4.65	ns
	DBP Mean ±SD (range)	84.4 ± 4.61	86.5 ± 5.32	88.1 ± 5.70	87.2 ± 4.58	82.4 ± 4.67	ns
Tonometry (mmHg) of eye before operation Mean ± SD (range)	15.3 ± 2.27	16.4 ± 3.42	17.8 ± 2.12	17.1 ± 2.82	16.3 ± 3.27	ns	

- Abbreviations: SD = Standard deviation, ns = not significant, PPBS = Post prandial blood sugar, BP = blood pressure, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, mg = milligram.
- p-values from Student’s unpaired t test.

It is also clear from the above Table 1 and Table 2 that each of the treatment arm was equivalent in terms of demographic profile and vital parameters among different subgroups.

Table 3 :Mean moxifloxacin level in Aqueous Humour and Plasma among all Groups :

GROUP	Time from last dose to sampling (hours)	Moxifloxacin level in aqueous humour (µg/ml) (Mean ± SD)	Moxifloxacin level in plasma (µg/ml) (Mean ± SD)
A	2	4.35 ± 0.24	7.58 ± 0.87
B	4	3.59 ± 0.34	5.91 ± 0.57
C	8	2.99 ± 0.09	3.56 ± 0.53
D	12	2.65 ± 0.20	2.89 ± 0.27
E	18	1.82 ± 0.32	2.61 ± 0.24

Figure 1 : Mean concentration of moxifloxacin in aqueous humour among different Groups over time :

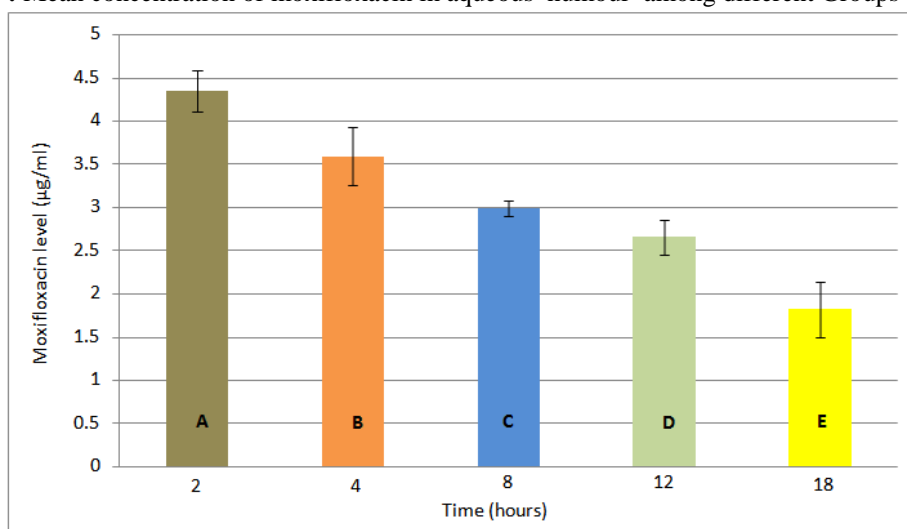


Figure 2 : Mean concentration of moxifloxacin in plasma among different Groups of over time :

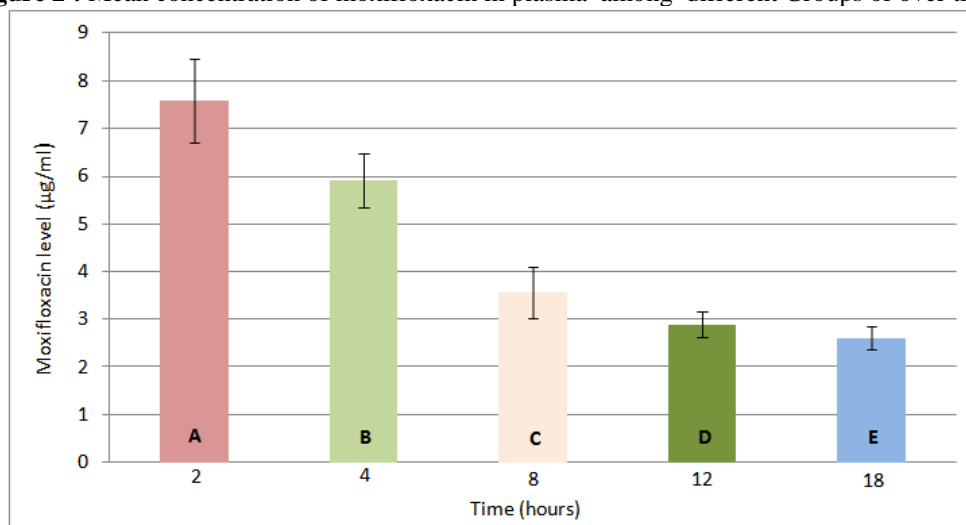


Table 3, Figure 1&2 depict the mean concentration of moxifloxacin in aqueous humour and plasma over time among different Groups. It was found that mean moxifloxacin level in aqueous humour ranged between $1.82 \pm 0.32 \mu\text{g/ml}$ (at 18 hour group) to $4.35 \pm 0.24 \mu\text{g/ml}$ (at 2 hour group) and maximum in 2 hours group (i.e. Group A) and least in Group E (i.e. 18 hours before sampling). Mean moxifloxacin level in plasma ranged between $2.61 \pm 0.24 \mu\text{g/ml}$ (at 18 hour group) to $7.58 \pm 0.87 \mu\text{g/ml}$ (at 2 hour group) and maximum in 2 hours group (i.e. Group A) and least in Group E (i.e. 18 hours before sampling).

From these data it was found that mean aqueous humour concentration of moxifloxacin rises to peak at the height of plasma level of moxifloxacin and gradually falls with time.

Treatment emergent adverse events :

Endophthalmitis was not found in any patient on first post-operative day. No adverse event after addition of oral moxifloxacin or any reactions with topical agents were reported. No complication due to aspiration of aqueous humour to any patient was found.

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